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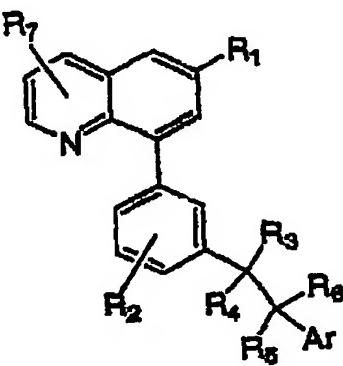
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(54) Title: **SUBSTITUTED 8-ARYLQUINOLINE PDE4 INHIBITORS**



(57) Abstract: 8-arylquinolines of formula(I) wherein the aryl group at the 8-position contains a *meta* two atom bridge to an optionally substituted phenyl or pyridyl group, are PDE4 inhibitors useful to treat asthma, chronic bronchitis, chronic obstructive pulmonary disease, arthritis, respiratory distress syndrome, allergic rhinitis, neurogenic inflammation, pain, rheumatoid arthritis, and other diseases. R¹-R⁷ and Ar are as in claim 1.

TITLE OF THE INVENTION**SUBSTITUTED 8-ARYLQUINOLINE PDE4 INHIBITORS****5 BACKGROUND OF THE INVENTION****FIELD OF THE INVENTION**

The present invention is directed to compounds that are substituted 8-arylquinolines. In particular, this invention is directed to substituted 8-arylquinolines which are phosphodiesterase-4 inhibitors wherein the aryl group at the 8-position contains a *meta* two carbon atom bridge to an optionally substituted phenyl or pyridyl group.

RELATED BACKGROUND

Hormones are compounds that variously affect cellular activity. In many respects, hormones act as messengers to trigger specific cellular responses and activities. Many effects produced by hormones, however, are not caused by the singular effect of just the hormone. Instead, the hormone first binds to a receptor, thereby triggering the release of a second compound that goes on to affect the cellular activity. In this scenario, the hormone is known as the first messenger while the second compound is called the second messenger. Cyclic adenosine monophosphate (adenosine 3', 5'-cyclic monophosphate, "cAMP" or "cyclic AMP") is known as a second messenger for hormones including epinephrine, glucagon, calcitonin, corticotrophin, lipotropin, luteinizing hormone, norepinephrine, parathyroid hormone, thyroid-stimulating hormone, and vasopressin. Thus, cAMP mediates cellular responses to hormones. Cyclic AMP also mediates cellular responses to various neurotransmitters.

Phosphodiesterases ("PDE") are a family of enzymes that metabolize 3', 5' cyclic nucleotides to 5' nucleoside monophosphates, thereby terminating cAMP second messenger activity. A particular phosphodiesterase, phosphodiesterase-4 ("PDE4", also known as "PDE-IV"), which is a high affinity, cAMP specific, type IV PDE, has generated interest as potential targets for the development of novel anti-asthmatic and anti-inflammatory compounds. PDE4 is known to exist as at least four isoenzymes, each of which is encoded by a distinct gene. Each of the four known PDE4 gene products is believed to play varying roles in allergic and/or inflammatory

responses. Thus, it is believed that inhibition of PDE4, particularly the specific PDE4 isoforms that produce detrimental responses, can beneficially affect allergy and inflammation symptoms. It would be desirable to provide novel compounds and compositions that inhibit PDE4 activity.

5 Inhibition of PDE4 activity is believed effective for the treatment of osteoporosis by reducing bone loss. For example, Ken-ici Miyamoto et al., *Biochem. Pharmacology*, 54:613-617(1997) describes the effect of a PDE4 on bone loss.

Therefore, it would be desirable to provide novel compounds and compositions that inhibit PDE4 activity.

10 A major concern with the use of PDE4 inhibitors is the side effect of emesis which has been observed for several candidate compounds as described in C.Burnouf et al. *Ann. Rep. In Med. Chem.*, 33:91-109(1998). B.Hughes et al., *Br. J.Pharmacol.*, 118:1183-1191(1996); M.J.Perry et al., *Cell Biochem. Biophys.*, 29:113-132(1998); S.B.Christensen et al., *J.Med. Chem.*, 41:821-835(1998); and

15 Burnouf (*Ibid.*) describe the wide variation of the severity of the undesirable side effects exhibited by various compounds. As described in M.D.Houslay et al., *Adv. In Pharmacol.*, 44:225-342(1998) and D.Spina et al., *Adv. In Pharmacol.*, 44:33-89(1998), there is great interest and research of therapeutic PDE4 inhibitors.

International Patent Publication WO9422852 describes quinolines as
20 PDE4 inhibitors.

25 A.H.Cook, et al., *J.Chem. Soc.*, 413-417(1943) describes gamma-pyridylquinolines. Other quinoline compounds are described in Kei Manabe et al., *J.Org. Chem.*, 58(24):6692-6700(1993); Kei Manabe et al., *J.Am. Chem. Soc.*, 115(12):5324-5325(1993); and Kei Manabe et al., *J.Am. Chem. Soc.*, 114(17):6940-6941(1992).

Compounds that include ringed systems are described by various investigators as effective for a variety of therapies and utilities. For example, International Patent Publication No. WO 98/25883 describes ketobenzamides as calpain inhibitors, European Patent Publication No. EP 811610 and U.S. Patent Nos. 30 5,679,712, 5,693,672 and 5,747,541 describe substituted benzoylguanidine sodium channel blockers, U.S. Patent No. 5,736,297 describes ring systems useful as a photosensitive composition.

35 U.S. Patent Nos. 5,491,147, 5,608,070, 5,622,977, 5,739,144, 5,776,958, 5,780,477, 5,786,354, 5,798,373, 5,849,770, 5,859,034, 5,866,593, 5,891,896, and International Patent Publication WO 95/35283 describe PDE4

inhibitors that are tri-substituted aryl or heteroaryl phenyl derivatives. U.S. Patent No. 5,580,888 describes PDE4 inhibitors that are styryl derivatives. U.S. Patent No. 5,550,137 describes PDE4 inhibitors that are phenylaminocarbonyl derivatives. U.S. Patent No. 5,340,827 describes PDE4 inhibitors that are phenylcarboxamide compounds. U.S. Patent No. 5,780,478 describes PDE4 inhibitors that are tetra-substituted phenyl derivatives. International Patent Publication WO 96/00215 describes substituted oxime derivatives useful as PDE4 inhibitors. U.S. Patent No. 5,633,257 describes PDE4 inhibitors that are cyclo(alkyl and alkenyl)phenyl-alkenyl (aryl and heteroaryl) compounds.

10 However, there remains a need for novel compounds and compositions that therapeutically inhibit PDE4 with minimal side effects.

SUMMARY OF THE INVENTION

15 The present invention is directed to novel substituted 8-arylquinolines that are PDE4 inhibitors, wherein the aryl group at the 8-position contains a *meta* two carbon atom bridge to an optionally substituted phenyl or pyridyl group. This invention also provides a pharmaceutical composition which includes an effective amount of the novel substituted 8-arylquinoline and a pharmaceutically acceptable carrier.

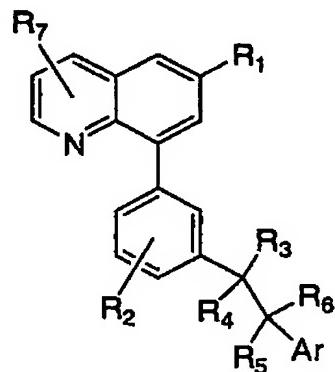
20 This invention further provides a method of treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, 25 reperfusion injury of the myocardium and brain, inflammatory arthritis, osteoporosis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, infant respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, atherosclerosis, neurogenic inflammation, pain, 30 cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, monopolar depression, acute and chronic neurodegenerative disorders 35 with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord

trauma, head injury, multiple sclerosis, tumour growth and cancerous invasion of normal tissues by the administration of an effective amount of the novel substituted 8-arylquinoline or a precursor compound which forms *in vivo* the novel substituted 8-arylquinoline.

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DETAILED DESCRIPTION OF THE INVENTION

A compound of this invention is represented by Formula (I):



(I)

- 10 or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, pyridinone, pyridyl, or pyridyl N-oxide, optionally substituted with 1-5 independent -C₁₋₆alkyl, -OH, -CN, halogen, -CF₃, -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl), -(C₀₋₆alkyl)-SO_n-NH-(C₁₋₆alkyl) or 5-membered

- 15 heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁₋₆alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

20 R₁ is hydrogen, halogen; or a -C₁₋₆alkyl, -cycloC₃₋₆alkyl, -C₁₋₆alkenyl, -C₀₋₄alkyl-C(O)-C₀₋₄alkyl, -C₁₋₆alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃₋₆alkyl, -amino, -C₁₋₆alkylamino, -(C₁₋₆alkyl)(C₁₋₆alkyl)amino, -C₁₋₆alkyl(oxy)C₁₋₆alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁₋₆alkyl), -C(O)N(C₀₋₆alkyl)(C₀₋₆alkyl), -NH-SO_n-(C₁₋₆alkyl), -carbamoyl, -(C₁₋₆alkyl)-O-C(CN)-dialkylamino, or -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl,

- alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);
- R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or OH;
- 5 R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁-6alkyl, or C₁-6alkyl substituents, and the alkyl group is optionally substituted with OH
- 10 R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)₂, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)₂, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)₂, -P(O)(C₁-6alkyl)₂, -P(O)(C₁-6alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents;
- 15 or R₅ and R₆ form =O;
- 20 or R₆ and R₃ form -CH₂- or -O-; and
- n is 0, 1, or 2.

- In one aspect, the compound of this invention is represented by
- 25 Formula (I) or a pharmaceutically acceptable salt thereof, wherein Ar is phenyl, optionally substituted with 1-3 independent -C₁-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C₁-6alkyl), -(C₀-6alkyl)-SO_n-NH-(C₁-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with 30 C₁-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -C₁-6alkyl, and halogen, or -CF₃;
- R₁ is hydrogen, halogen; or a -C₁-6alkyl, -cycloC₃-6alkyl, -C₁-6alkenyl, -C₀-4alkyl-C(O)-C₀-4alkyl, -C₁-6alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃-6alkyl, -amino, -C₁-6alkylamino, -(C₁-6alkyl)(C₁-6alkyl)amino,

- C₁₋₆alkyl(oxy)C₁₋₆alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁₋₆alkyl), -C(O)N(C₀₋₆alkyl)(C₀₋₆alkyl), -NH-SO_n-(C₁₋₆alkyl), -carbamoyl, -(C₁₋₆alkyl)-O-C(CN)-dialkylamino, or -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl) group, wherein any of the groups is optionally substituted
- 5 with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃₋₆alkyl, heterocycloC₃₋₆alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁₋₆alkyl);
- R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁₋₆alkyl, or -C₁₋₆alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;
- 10 R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁₋₆alkyl, or C₁₋₆alkyl
- 15 substituents, and the alkyl group is optionally substituted with OH;
- R₅ is hydrogen, hydroxyl, -CN; or a -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀₋₆alkyl, -C(O)-C₃₋₇cycloalkyl, -C₁₋₆alkyl-C₃₋₇cycloalkyl, -C₁₋₆alkyl(C₃₋₇cycloalkyl)₂, -C₁₋₆alkyl-aryl, -C(O)-N(C₀₋₆alkyl)₂, -SO_naryl, -SO_n-C₁₋₆alkyl, -SO_n-C₃₋₇cycloalkyl, -SO_n-N(C₀₋₆alkyl)₂,
- 20 -P(O)(C₁₋₆alkyl)₂, -P(O)(C₁₋₆alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁₋₆alkyl, -SO_n-C₁₋₆alkyl, -C(O)-O-C₀₋₆alkyl, or hydroxyC₁₋₆alkyl substituents;
- 25 or R₅ and R₆ form =O;
or R₆ and R₃ form -CH₂₋ or -O-; and
n is 0, 1, or 2.

In an embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein Ar is phenyl, optionally substituted with 1-3 independent -C₁₋₆alkyl, -OH, -CN, halogen, -CF₃, -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl), -(C₀₋₆alkyl)-SO_n-NH-(C₁₋₆alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with

$C_1\text{-}6$ alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

- R₁ is hydrogen, halogen; or a -C₁-6alkyl, -cycloC₃-6alkyl, -C₁-6alkenyl, -C₀-4alkyl-C(O)-C₀-4alkyl, -C₁-6alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃-6alkyl, -amino, -C₁-6alkylamino, -(C₁-6alkyl)(C₁-6alkyl)amino, -C₁-6alkyl(oxy)C₁-6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁-6alkyl), -C(O)N(C₀-6alkyl)(C₀-6alkyl), -NH-SO_n-(C₁-6alkyl), -carbamoyl, -(C₁-6alkyl)-O-C(CN)-dialkylamino, or -(C₀-6alkyl)-SO_n-(C₁-6alkyl) group, wherein any of the groups is optionally substituted 5 with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);
- 10 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;
- 15 R₄ is hydrogen, halogen, -CN, or -C(O)-O-C₀-6alkyl, wherein the -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁-6alkyl, or C₁-6alkyl substituents, and the alkyl group is optionally 20 substituted with OH;
- 20 R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)2, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)2, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)2, 25 -P(O)(C₁-6alkyl)2, -P(O)(C₁-6alkoxy)2, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or Nor oxoisoxaphosphinanyl group, any of which group 30 optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents; or R₅ and R₆ form =O; or R₆ and R₃ form -CH₂- or -O-; and n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

- Ar is phenyl, optionally substituted with 1-3 independent -C₁₋₆alkyl,
5 -OH, -CN, halogen, -CF₃, -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl), -(C₀₋₆alkyl)-SO_n-NH-(C₁₋₆alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁₋₆alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;
- 10 R₁ is hydrogen, halogen; or a -C₁₋₆alkyl, -cycloC₃₋₆alkyl, -C₁₋₆alkenyl, -C₀₋₄alkyl-C(O)-C₀₋₄alkyl, -C₁₋₆alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃₋₆alkyl, -amino, -C₁₋₆alkylamino, -(C₁₋₆alkyl)(C₁₋₆alkyl)amino, -C₁₋₆alkyl(oxy)C₁₋₆alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁₋₆alkyl), -C(O)N(C₀₋₆alkyl)(C₀₋₆alkyl),
15 -NH-SO_n-(C₁₋₆alkyl), -carbamoyl, -(C₁₋₆alkyl)-O-C(CN)-dialkylamino, or -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃₋₆alkyl, heterocycloC₃₋₆alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁₋₆alkyl);
20 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁₋₆alkyl, or -C₁₋₆alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;
- R₄ is oxadiazolyl optionally substituted with 1-3 independent halogen, 25 CN, CF₃, -SO_n-C₁₋₆alkyl, or C₁₋₆alkyl substituents, and the alkyl group is optionally substituted with OH;
- R₅ is hydrogen, hydroxyl, -CN; or a -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀₋₆alkyl, -C(O)-C₃₋₇cycloalkyl, -C₁₋₆alkyl-C₃₋₇cycloalkyl, -C₁₋₆alkyl(C₃₋₇cycloalkyl)₂, -C₁₋₆alkyl-aryl, -C(O)-N(C₀₋₆alkyl)₂, -SO_naryl, -SO_n-C₁₋₆alkyl, -SO_n-C₃₋₇cycloalkyl, -SO_n-N(C₀₋₆alkyl)₂, -P(O)(C₁₋₆alkyl)₂, -P(O)(C₁₋₆alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁₋₆alkyl, -SO_n-C₁₋₆alkyl, -C(O)-O-C₀₋₆alkyl, or hydroxyC₁₋₆alkyl substituents;
30
35

or R₅ and R₆ form =O;
 or R₆ and R₃ form -CH₂- or -O-; and
 n is 0, 1, or 2.

5 In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

10 Ar is phenyl, optionally substituted with 1-3 independent -C₁₋₆alkyl, -OH, -CN, halogen, -CF₃, -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl), -(C₀₋₆alkyl)-SO_n-NH-(C₁₋₆alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁₋₆alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

15 R₁ is hydrogen, halogen; or a -C₁₋₆alkyl, -cycloC₃₋₆alkyl, -C₁₋₆alkenyl, -C₀₋₄alkyl-C(O)-C₀₋₄alkyl, -C₁₋₆alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃₋₆alkyl, -amino, -C₁₋₆alkylamino, -(C₁₋₆alkyl)(C₁₋₆alkyl)amino, -C₁₋₆alkyl(oxy)C₁₋₆alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁₋₆alkyl), -C(O)N(C₀₋₆alkyl)(C₀₋₆alkyl), -NH-SO_n-(C₁₋₆alkyl), -carbamoyl, -(C₁₋₆alkyl)-O-C(CN)-dialkylamino, or -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C₁₋₆alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃₋₆alkyl, heterocycloC₃₋₆alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁₋₆alkyl);

20 25 R₂ and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁₋₆alkyl, or -C₁₋₆alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

25 30 R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁₋₆alkyl, or C₁₋₆alkyl substituents, and the alkyl group is optionally substituted with OH;

R₅ is hydrogen, hydroxyl, -CN; or a -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀₋₆alkyl, -C(O)-C₃₋₇cycloalkyl, -C₁₋₆alkyl-

- C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)2, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)2, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)2, -P(O)(C₁-6alkyl)2, -P(O)(C₁-6alkoxy)2, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents;
- 5 R₆ and R₃ form -CH₂-; and
n is 0, 1, or 2.

10

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein Ar is phenyl, optionally substituted with 1-3 independent -C₁-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C₁-6alkyl), -(C₀-6alkyl)-SO_n-NH-(C₁-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

15 R₁ is -C₁-6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);

20 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

25 R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁-6alkyl, or C₁-6alkyl substituents, and the alkyl group is optionally substituted with OH

30 R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)2, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)2, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)2,

-P(O)(C₁-6alkyl)₂, -P(O)(C₁-6alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents; 5 or R₅ and R₆ form =O; or R₆ and R₃ form -CH₂- or -O-; and n is 0, 1, or 2.

10 In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, optionally substituted with 1-3 independent -C₁-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C₁-6alkyl), -(C₀-6alkyl)-SO_n-NH-(C₁-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

15 R₁ is -C₁-6alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);

20 R₂, and R₃ are each hydrogen;

25 R₄ is hydrogen;

R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C(O)-aryl, -C(O)-N(C₀-C₃-7cycloalkyl), -C₁-6alkyl(C₃-7cycloalkyl)₂, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)₂, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)₂, -P(O)(C₁-6alkyl)₂, -P(O)(C₁-6alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents;

R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;
 or R₅ and R₆ form =O;
 5 or R₆ and R₃ form -CH₂- or -O-; and
 n is 0, 1, or 2.

In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof,
 10 wherein

Ar is phenyl substituted with -(C₀-6alkyl)-SO_n-(C₁-6alkyl), and the alkyl group is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

R₁ is -C₁-6alkyl, optionally substituted with 1-5 substituents; wherein
 15 each substituent is independently a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);

R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁-6alkyl, or C₁-6alkyl substituents, and the alkyl group is optionally substituted with OH

R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)₂, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)₂, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)₂, -P(O)(C₁-6alkyl)₂, -P(O)(C₁-6alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents;

or R₅ and R₆ form =O;
 or R₆ and R₃ form -CH₂- or -O-; and
 n is 0, 1, or 2.

5 In still another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

10 Ar is phenyl substituted with -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl), and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

15 R₁ is -C₁₋₆alkyl, optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃₋₆alkyl, heterocycloC₃₋₆alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁₋₆alkyl);

R₂ and R₃ are each hydrogen;

R₄ is hydrogen;

20 R₅ is hydrogen, hydroxyl, -CN; or a -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀₋₆alkyl, -C(O)-C₃₋₇cycloalkyl, -C₁₋₆alkyl-C₃₋₇cycloalkyl, -C₁₋₆alkyl(C₃₋₇cycloalkyl)₂, -C₁₋₆alkyl-aryl, -C(O)-N(C₀₋₆alkyl)₂, -SO_naryl, -SO_n-C₁₋₆alkyl, -SO_n-C₃₋₇cycloalkyl, -SO_n-N(C₀₋₆alkyl)₂, -P(O)(C₁₋₆alkyl)₂, -P(O)(C₁₋₆alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N group or oxoisoaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁₋₆alkyl, -SO_n-C₁₋₆alkyl, -C(O)-O-C₀₋₆alkyl, or hydroxyC₁₋₆alkyl substituents;

25 R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁₋₆alkyl, or -C₁₋₆alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

30 or R₅ and R₆ form =O;

or R₆ and R₃ form -CH₂- or -O-; and

n is 0, 1, or 2.

In a second aspect of the invention, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

Ar is pyridyl, or pyridyl N-oxide, optionally substituted with 1-3 independent -C₁₋₆alkyl, -OH, -CN, halogen, -CF₃, -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl),

- 5 -(C₀₋₆alkyl)-SO_n-NH-(C₁₋₆alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁₋₆alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

R₁ is hydrogen, halogen; or a -C₁₋₆alkyl, -cycloC₃₋₆alkyl,

- 10 -C₁₋₆alkenyl, -C₀₋₄alkyl-C(O)-C₀₋₄alkyl, -C₁₋₆alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃₋₆alkyl, -amino, -C₁₋₆alkylamino, -(C₁₋₆alkyl)(C₁₋₆alkyl)amino, -C₁₋₆alkyl(oxy)C₁₋₆alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁₋₆alkyl), -C(O)N(C₀₋₆alkyl)(C₀₋₆alkyl), -NH-SO_n-(C₁₋₆alkyl), -carbamoyl, -(C₁₋₆alkyl)-O-C(CN)-dialkylamino, or -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃₋₆alkyl, heterocycloC₃₋₆alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁₋₆alkyl);

- 15 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁₋₆alkyl, or -C₁₋₆alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

- 20 R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁₋₆alkyl, or C₁₋₆alkyl substituents, and the alkyl group is optionally substituted with OH;

- 25 R₅ is hydrogen, hydroxyl, -CN; or a -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀₋₆alkyl, -C(O)-C₃₋₇cycloalkyl, -C₁₋₆alkyl-C₃₋₇cycloalkyl, -C₁₋₆alkyl(C₃₋₇cycloalkyl)₂, -C₁₋₆alkyl-aryl, -C(O)-N(C₀₋₆alkyl)₂, -SO_naryl, -SO_n-C₁₋₆alkyl, -SO_n-C₃₋₇cycloalkyl, -SO_n-N(C₀₋₆alkyl)₂, -P(O)(C₁₋₆alkyl)₂, -P(O)(C₁₋₆alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁₋₆alkyl, -SO_n-C₁₋₆alkyl, -C(O)-O-C₀₋₆alkyl, or hydroxyC₁₋₆alkyl substituents;

or R₅ and R₆ form =O;
 or R₆ and R₃ form -CH₂- or -O-; and
 n is 0, 1, or 2.

- 5 In an embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein Ar is pyridyl, or pyridyl N-oxide, optionally substituted with 1-3 independent -C₁₋₆alkyl, -OH, -CN, halogen, -CF₃, -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl), -(C₀₋₆alkyl)-SO_n-NH-(C₁₋₆alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁₋₆alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;
- 10 R₁ is hydrogen, halogen; or a -C₁₋₆alkyl, -cycloC₃₋₆alkyl, -C₁₋₆alkenyl, -C₀₋₄alkyl-C(O)-C₀₋₄alkyl, -C₁₋₆alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃₋₆alkyl, -amino, -C₁₋₆alkylamino, -(C₁₋₆alkyl)(C₁₋₆alkyl)amino, -C₁₋₆alkyl(oxy)C₁₋₆alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁₋₆alkyl), -C(O)N(C₀₋₆alkyl)(C₀₋₆alkyl), -NH-SO_n-(C₁₋₆alkyl), -carbamoyl, -(C₁₋₆alkyl)-O-C(CN)-dialkylamino, or -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃₋₆alkyl, heterocycloC₃₋₆alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁₋₆alkyl);
- 15 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁₋₆alkyl, or -C₁₋₆alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;
- 20 R₄ is phenyl optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁₋₆alkyl, or C₁₋₆alkyl substituents, and the alkyl group is optionally substituted with OH;
- 25 R₅ is hydrogen, hydroxyl, -CN; or a -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀₋₆alkyl, -C(O)-C₃₋₇cycloalkyl, -C₁₋₆alkyl-C₃₋₇cycloalkyl, -C₁₋₆alkyl(C₃₋₇cycloalkyl)₂, -C₁₋₆alkyl-aryl, -C(O)-N(C₀₋₆alkyl)₂, -SO_naryl, -SO_n-C₁₋₆alkyl, -SO_n-C₃₋₇cycloalkyl, -SO_n-N(C₀₋₆alkyl)₂, -P(O)(C₁₋₆alkyl)₂, -P(O)(C₁₋₆alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl,

- SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents;
- 5 or R₅ and R₆ form =O;
 or R₆ and R₃ form -CH₂- or -O-; and
 n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this
 10 invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

- Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent -C₁-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C₁-6alkyl), -(C₀-6alkyl)-SO_n-NH-(C₁-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;
- 15 R₁ is hydrogen, halogen; or a -C₁-6alkyl, -cycloC₃-6alkyl, -C₁-6alkenyl, -C₀-4alkyl-C(O)-C₀-4alkyl, -C₁-6alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃-6alkyl, -amino, -C₁-6alkylamino, -(C₁-6alkyl)(C₁-6alkyl)amino, -C₁-6alkyl(oxy)C₁-6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁-6alkyl), -C(O)N(C₀-6alkyl)(C₀-6alkyl), -NH-SO_n-(C₁-6alkyl), -carbamoyl, -(C₁-6alkyl)-O-C(CN)-dialkylamino, or -(C₀-6alkyl)-SO_n-(C₁-6alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);
- 20 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;
- 25 R₄ is hydrogen, halogen, -CN, or -C(O)-O-C₀-6alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl is optionally substituted with 1-3

independent halogen, CN, CF₃, -SO_n-C₁₋₆alkyl, or C₁₋₆alkyl substituents, and the alkyl group is optionally substituted with OH;

R₅ is hydrogen, hydroxyl, -CN; or a -C₁₋₆alkyl, -C(O)C₁₋₆alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀₋₆alkyl, -C(O)-C₃₋₇cycloalkyl, -C₁₋₆alkyl-

- 5 -C₃₋₇cycloalkyl, -C₁₋₆alkyl(C₃₋₇cycloalkyl)₂, -C₁₋₆alkyl-aryl, -C(O)-N(C₀₋₆alkyl)₂, -SO_naryl, -SO_n-C₁₋₆alkyl, -SO_n-C₃₋₇cycloalkyl, -SO_n-N(C₀₋₆alkyl)₂, -P(O)(C₁₋₆alkyl)₂, -P(O)(C₁₋₆alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group
- 10 optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁₋₆alkyl, -SO_n-C₁₋₆alkyl, -C(O)-O-C₀₋₆alkyl, or hydroxyC₁₋₆alkyl substituents; or R₅ and R₆ form =O; or R₆ and R₃ form -CH₂- or -O-; and n is 0, 1, or 2.

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In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

- Ar is pyridyl, or pyridyl N-oxide, optionally substituted with 1-3 independent -C₁₋₆alkyl, -OH, -CN, halogen, -CF₃, -(C₀₋₆alkyl)-SO_n(C₁₋₆alkyl), -(C₀₋₆alkyl)-SO_n-NH-(C₁₋₆alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁₋₆alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

25

R₁ is hydrogen, halogen; or a -C₁₋₆alkyl, -cycloC₃₋₆alkyl, -C₁₋₆alkenyl, -C₀₋₄alkyl-C(O)-C₀₋₄alkyl, -C₁₋₆alkoxy, aryl, heteroaryl, -CN, -heterocycloC₃₋₆alkyl, -amino, -C₁₋₆alkylamino, -(C₁₋₆alkyl)(C₁₋₆alkyl)amino, -C₁₋₆alkyl(oxy)C₁₋₆alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C₁₋₆alkyl), -C(O)N(C₀₋₆alkyl)(C₀₋₆alkyl), -NH-SO_n-(C₁₋₆alkyl), -carbamoyl, -(C₁₋₆alkyl)-O-C(CN)-dialkylamino, or -(C₀₋₆alkyl)-SO_n-(C₁₋₆alkyl) group, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl,

30 -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl,

alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);

R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁-6alkyl, or C₁-6alkyl substituents, and the alkyl group is optionally substituted with OH;

- 10 R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)₂, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)₂, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)₂, -P(O)(C₁-6alkyl)₂, -P(O)(C₁-6alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents;
- 15 or R₅ and R₆ form =O;
- 20 or R₆ and R₃ form -O-; and
- n is 0, 1, or 2.

In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

- 25 Ar is pyridyl, or pyridyl N-oxide, optionally substituted with 1-3 independent -C₁-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C₁-6alkyl), -(C₀-6alkyl)-SO_n-NH-(C₁-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;
- 30 R₁ is -C₁-6alkyl or -cycloC₃-6alkyl, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-

$\text{C}_1\text{-alkyl}$), $-\text{C}(\text{O})-\text{O}-\text{aryl}$, alkoxy, cycloalkyloxy, acyl, acyloxy, $-\text{cycloC}_3\text{-alkyl}$, heterocycloC₃-alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or $-\text{SO}_n-(\text{C}_1\text{-alkyl})$;

5 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, $-\text{C}_1\text{-alkyl}$, or $-\text{C}_1\text{-alkoxy}$, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

10 R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or $-\text{C}(\text{O})-\text{O}-\text{C}_0\text{-alkyl}$, wherein the phenyl, oxadiazolyl, or $-\text{C}(\text{O})-\text{O}-\text{C}_0\text{-alkyl}$ is optionally substituted with 1-3 independent halogen, CN, CF₃, $-\text{SO}_n-\text{C}_1\text{-alkyl}$, or C₁-alkyl substituents, and the alkyl group is optionally substituted with OH;

15 R₅ is hydrogen, hydroxyl, -CN; or a $-\text{C}_1\text{-alkyl}$, $-\text{C}(\text{O})\text{C}_1\text{-alkyl}$, $-\text{C}(\text{O})-\text{aryl}$, $-\text{C}(\text{O})-\text{pyridyl}$, $-\text{C}(\text{O})-\text{O}-\text{C}_0\text{-alkyl}$, $-\text{C}(\text{O})-\text{C}_3\text{-7cycloalkyl}$, $-\text{C}_1\text{-alkyl-C}_3\text{-7cycloalkyl}$, $-\text{C}_1\text{-alkyl}(\text{C}_3\text{-7cycloalkyl})_2$, $-\text{C}_1\text{-alkyl-aryl}$, $-\text{C}(\text{O})-\text{N}(\text{C}_0\text{-alkyl})_2$, $-\text{SO}_n\text{aryl}$, $-\text{SO}_n-\text{C}_1\text{-alkyl}$, $-\text{SO}_n-\text{C}_3\text{-7cycloalkyl}$, $-\text{SO}_n-\text{N}(\text{C}_0\text{-alkyl})_2$, $-\text{P}(\text{O})(\text{C}_1\text{-alkyl})_2$, $-\text{P}(\text{O})(\text{C}_1\text{-alkoxy})_2$, phenyl, pyridyl, $-\text{SO}_n\text{imidazolyl}$, $-\text{SO}_n\text{thiazolyl}$, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, $-\text{C}_1\text{-alkyl}$, $-\text{SO}_n-\text{C}_1\text{-alkyl}$, $-\text{C}(\text{O})-\text{O}-\text{C}_0\text{-alkyl}$, or hydroxyC₁-alkyl substituents;

20 or R₅ and R₆ form =O;

 or R₆ and R₃ form $-\text{CH}_2-$ or $-\text{O}-$; and

 n is 0, 1, or 2.

25 In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

30 Ar is pyridyl, or pyridyl N-oxide, optionally substituted with 1-3 independent $-\text{C}_1\text{-alkyl}$, -OH, -CN, halogen, -CF₃, $-(\text{C}_0\text{-alkyl})-\text{SO}_n-(\text{C}_1\text{-alkyl})$, $-(\text{C}_0\text{-alkyl})-\text{SO}_n-\text{NH}-(\text{C}_1\text{-alkyl})$ or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁-alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

 R₁ is $-\text{C}_1\text{-alkyl}$, $-\text{cycloC}_3\text{-alkyl}$, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently

a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl *N*-oxide, carbonyl, carbamoyl, or -SO_n-(C₁-6alkyl);

5 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁-6alkyl, or -C₁-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;

10 R₄ is hydrogen, halogen, -CN, or -C(O)-O-C₀-6alkyl, wherein the -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁-6alkyl, or C₁-6alkyl substituents, and the alkyl group is optionally substituted with OH

15 R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)₂, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)₂, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)₂, -P(O)(C₁-6alkyl)₂, -P(O)(C₁-6alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents; or R₅ and R₆ form =O; or R₆ and R₃ form -CH₂- or -O-; and n is 0, 1, or 2.

25 In another embodiment of this one aspect, the compound of this invention is represented by Formula (I) or a pharmaceutically acceptable salt thereof, wherein

30 Ar is pyridyl, or pyridyl *N*-oxide, optionally substituted with 1-3 independent -C₁-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C₁-6alkyl), -(C₀-6alkyl)-SO_n-NH-(C₁-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

- R₁ is -C₁₋₆alkyl, -cycloC₃₋₆alkyl, wherein any of the groups is optionally substituted with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C_{1-C6}alkyl, -C(O)(heterocycloC₃₋₆alkyl), -C(O)-O-(C₀₋₆alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃₋₆alkyl, heterocycloC₃₋₆alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C₁₋₆alkyl);
- 5 R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen, hydroxyl, -C₁₋₆alkyl, or -C₁₋₆alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or hydroxyl;
- 10 R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀₋₆alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁₋₆alkyl, or C₁₋₆alkyl substituents, and the alkyl group is optionally substituted with OH
- 15 R₅ is phenyl, pyridyl, or a 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁₋₆alkyl, -SO_n-C₁₋₆alkyl, -C(O)-O-C₀₋₆alkyl, or hydroxyC₁₋₆alkyl substituents;
- or R₅ and R₆ form =O;
- or R₆ and R₃ form -CH₂₋ or -O-; and
- 20 n is 0, 1, or 2.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-

tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

5 The term "aryl" means an aromatic substituent which is a single ring or multiple rings fused together. When formed of multiple rings, at least one of the constituent rings is aromatic. The preferred aryl substituents are phenyl and naphthyl groups.

10 The term "cycloalkyloxy" unless specifically stated otherwise includes a cycloalkyl group connected by a short C₁₋₂alkyl length to the oxy connecting atom.

 The term "C₀₋₆alkyl" includes alkyls containing 6, 5, 4, 3, 2, 1, or no carbon atoms. An alkyl with no carbon atoms is a hydrogen atom substituent when the alkyl is a terminal group and is a direct bond when the alkyl is a bridging group.

15 The term "hetero" unless specifically stated otherwise includes one or more O, S, or N atoms. For example, heterocycloalkyl and heteroaryl include ring systems that contain one or more O, S, or N atoms in the ring, including mixtures of such atoms. The hetero atoms replace ring carbon atoms. Thus, for example, a heterocycloC₅alkyl is a five member ring containing from 5 to no carbon atoms.

20 Examples of heteroaryls include pyridinyl, quinolinyl, isoquinolinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinoxalinyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, pyrrolyl, indolyl, pyrazolyl, indazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, and tetrazolyl. Examples of heterocycloalkyls include azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydrofuran, imidazolinyl, pyrrolidin-2-one, piperidin-2-one, and thiomorpholinyl.

25 The term "amine" unless specifically stated otherwise includes primary, secondary and tertiary amines.

 The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

30 The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring. Further, optionally substituted multiple moieties such as, for example, alkylaryl are intended to mean that the aryl and the aryl groups are optionally substituted. If only one of the multiple moieties is

optionally substituted then it will be specifically recited such as "an alkylaryl, the aryl optionally substituted with halogen or hydroxyl."

Compounds described herein contain one or more double bonds and may thus give rise to cis/trans isomers as well as other conformational isomers. The present invention includes all such possible isomers as well as mixtures of such isomers.

Compounds described herein can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included.

During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (Ic andous), ferric, ferrous, lithium, magnesium, manganese (Ic andous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins,

procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. Such additional therapeutic ingredients include, for example, i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, iii) corticosteroids, iv) H1 receptor antagonists, v) beta 2 adrenoceptor agonists, vi) COX-2 selective inhibitors, vii) statins, viii) non-steroidal anti-inflammatory drugs ("NSAID"), and ix) M2/M3 antagonists. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

Creams, ointments, jellies, solutions, or suspensions containing the compound of Formula I can be employed for topical use. Mouth washes and gargles are included within the scope of topical use for the purposes of this invention.

Dosage levels from about 0.01mg/kg to about 140mg/kg of body weight per day are useful in the treatment of conditions such as asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals,

diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced 5 sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues which are responsive to PDE4 inhibition, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammation may be effectively treated by the administration 10 of from about 0.01mg to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day. Further, it is understood that the PDE4 inhibiting compounds of this invention can be administered at prophylactically effective dosage levels to prevent the above-recited conditions.

The amount of active ingredient that may be combined with the carrier 15 materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may conveniently contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total 20 composition. Unit dosage forms will generally contain between from about 1mg to about 1000mg of the active ingredient, typically 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg or 1000mg.

It is understood, however, that the specific dose level for any particular 25 patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

In practice, the compounds represented by Formula I, or 30 pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the 35 active ingredient. Further, the compositions can be presented as a powder, as

granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or pharmaceutically acceptable salts thereof, may also be administered by controlled 5 release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid 10 carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts 15 thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid 20 carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used to form oral 25 liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers 30 are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable 35 machine, the active ingredient in a free-flowing form such as powder or granules,

optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.1mg to about 500mg of the active ingredient and

- 5 each cachet or capsule preferably containing from about 0.1mg to about 500mg of the active ingredient. Thus, a tablet, cachet, or capsule conveniently contains 0.1mg, 1mg, 5mg, 25mg, 50mg, 100mg, 200mg, 300mg, 400mg, or 500mg of the active ingredient taken one or two tablets, cachets, or capsules, once, twice, or three times daily.

10 Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be
15 included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final
20 injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene
25 glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a
30 compound represented by Formula I of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

The compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as PDE4 inhibitors. Accordingly, another aspect of the invention is the treatment in mammals of, for example, asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, endotoxic shock (and associated conditions such as laminitis and colic in horses), septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, atopic dermatitis, urticaria, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, rheumatoid arthritis, ankylosing spondylitis, transplant rejection and graft versus host disease, hypersecretion of gastric acid, bacterial, fungal or viral induced sepsis or septic shock, inflammation and cytokine-mediated chronic tissue degeneration, osteoarthritis, cancer, cachexia, muscle wasting, depression, memory impairment, tumour growth and cancerous invasion of normal tissues – maladies that are amenable to amelioration through inhibition of the PDE4 isoenzyme and the resulting elevated cAMP levels – by the administration of an effective amount of the compounds of this invention. The term "mammals" includes humans, as well as other animals such as, for example, dogs, cats, horses, pigs, and cattle. Accordingly, it is understood that the treatment of mammals other than

humans is the treatment of clinical correlating afflictions to those above recited examples that are human afflictions.

Further, as described above, the compound of this invention can be utilized in combination with other therapeutic compounds. In particular, the 5 combinations of the PDE4 inhibiting compound of this invention can be advantageously used in combination with i) Leukotriene receptor antagonists, ii) Leukotriene biosynthesis inhibitors, or iii) M2/M3 antagonists.

The abbreviations used herein have the following tabulated meanings. Abbreviations not tabulated below have their meanings as commonly used unless 10 specifically stated otherwise.

Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
BINAP	1,1'-bi-2-naphthol
Bn	benzyl
CAMP	cyclic adenosine-3',5'-monophosphate
DAST	(diethylamino)sulfur trifluoride
DEAD	diethyl azodicarboxylate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	N,N-dimethylformamide
dppf	1,1'-bis(diphenylphosphino)-ferrocene
EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
Et₃N	triethylamine
GST	glutathione transferase
HMDS	hexamethyldisilazide
LDA	lithium diisopropylamide
m-CPBA	metachloroperbenzoic acid
MMPP	monoperoxyphthalic acid
MPPM	monoperoxyphthalic acid, magnesium salt 6H ₂ O
Ms	methanesulfonyl = mesyl = SO ₂ Me
MsO	methanesulfonate = mesylate

NBS	N-bromo succinimide
NSAID	non-steroidal anti-inflammatory drug
o-Tol	ortho-tolyl
OXONE®	2KHSO ₅ •KHSO ₄ •K ₂ SO ₄
PCC	pyridinium chlorochromate
Pd ₂ (dba) ₃	Bis(dibenzylideneacetone) palladium(0)
PDC	pyridinium dichromate
PDE	Phosphodiesterase
Ph	Phenyl
Phe	Benzenediyl
PMB	para-methoxybenzyl
Pye	Pyridinediyl
r.t.	room temperature
Rac.	Racemic
SAM	aminosulfonyl or sulfonamide or SO ₂ NH ₂
SEM	2-(trimethylsilyl)ethoxymethoxy
SPA	scintillation proximity assay
TBAF	tetra-n-butylammonium fluoride
Th	2- or 3-thienyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
THF	Tetrahydrofuran
Thi	Thiophenediyl
TLC	thin layer chromatography
TMS-CN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
Tz	1H (or 2H)-tetrazol-5-yl
XANTPHOS	4,5-Bis-diphenylphosphanyl-9,9-dimethyl-9H-xanthene
C ₃ H ₅	Allyl

ALKYL GROUP ABBREVIATIONS

Me	=	Methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

ASSAYS DEMONSTRATING BIOLOGICAL ACTIVITY

5

**LPS AND fMLP-INDUCED TNF- α AND LTB₄ ASSAYS IN HUMAN
WHOLE BLOOD**

Whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as PDE4-selective inhibitors. Normal non-stimulated human blood does not contain detectable levels of TNF- α and LTB₄. Upon stimulation with LPS, activated monocytes express and secrete TNF- α up to 8 hours and plasma levels remain stable for 24 hours. Published studies have shown that inhibition of TNF- α by increasing intracellular cAMP via PDE4 inhibition and/or enhanced adenylyl cyclase activity occurs at the transcriptional level. LTB₄ synthesis is also sensitive to levels of intracellular cAMP and can be completely inhibited by PDE4-selective inhibitors. As there is little LTB₄ produced during a 24 hour LPS stimulation of whole blood, an additional LPS stimulation followed by fMLP challenge of human whole blood is necessary for LTB₄ synthesis by activated neutrophils. Thus, by using the same blood sample, it is possible to evaluate the potency of a compound on two surrogate markers of PDE4 activity in the whole blood by the following procedure.

Fresh blood was collected in heparinized tubes by venipuncture from healthy human volunteers (male and female). These subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 4 days prior to blood collection. 500 μ L aliquots of blood were pre-incubated with either 2 μ L of vehicle (DMSO) or 2 μ L of test compound at varying concentrations for 15 minutes at 37°C. This was followed by the addition of either 10 μ L vehicle (PBS) as blanks or 10 μ L LPS (1 μ g/mL final concentration, #L-2630 (Sigma Chemical Co., St. Louis, MO) from *E. coli*, serotype 0111:B4; diluted in 0.1% w/v BSA (in PBS)). After 24 hours of incubation at 37°C, another 10 μ L of PBS (blank) or 10 μ L of LPS (1 μ g/mL final concentration) was added to blood and incubated for 30 minutes at 37°C. The blood was then challenged with either 10 μ L of PBS (blank) or 10 μ L of fMLP (1 μ M final concentration, #F-3506 (Sigma); diluted in 1% w/v BSA (in PBS)) for 15 minutes at 37°C. The blood samples were centrifuged at 1500xg for 10 minutes at 4°C to obtain plasma. A 50 μ L aliquot of plasma was mixed with 200 μ L methanol for protein precipitation and centrifuged as above. The supernatant was assayed for LTB₄ using an enzyme immunoassay kit (#520111 from Cayman Chemical Co., Ann Arbor, MI) according to the manufacturer's procedure. TNF- α was assayed in diluted plasma (in PBS) using an ELISA kit (Cistron Biotechnology, Pine Brook, NJ) according to manufacturer's procedure. The IC₅₀ values of Examples 1-113 generally ranged from 0.02 μ M to 26 μ M.

ANTI-ALLERGIC ACTIVITY IN VIVO

Compounds of the invention have been tested for effects on an IgE-mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs. Guinea pigs were initially sensitized to ovalbumin under mild cyclophosphamide-induced immunosuppression, by intraperitoneal injection of antigen in combinations with aluminum hydroxide and pertussis vaccine. Booster doses of antigen were given two and four weeks later. At six weeks, animals were challenged with aerosolized ovalbumin while under cover of an intraperitoneally administered anti-histamine agent (mepyramine). After a further 48h, bronchial alveolar lavages (BAL) were performed and the numbers of eosinophils and other leukocytes in the BAL fluids were counted. The lungs were also removed for histological examination for inflammatory damage. Administration of compounds of the Examples (0.001-10mg/kg i.p. or p.o.), up to three times during the 48h following antigen challenge, lead to a significant reduction in the eosinophilia and the

accumulation of other inflammatory leukocytes. There was also less inflammatory damage in the lungs of animals treated with compounds of the Examples.

SPA BASED PDE ACTIVITY ASSAY PROTOCOL

Compounds which inhibit the hydrolysis of cAMP to AMP by the type-IV cAMP-specific phosphodiesterases were screened in a 96-well plate format as follows:

In a 96 well-plate at 30°C was added the test compound (dissolved in 2µL DMSO), 188mL of substrate buffer containing [2,8-³H] adenosine 3',5'-cyclic phosphate (cAMP, 100nM to 50µM), 10mMmgCl₂, 1mM EDTA, 50mM Tris, pH 7.5. The reaction was initiated by the addition of 10mL of human recombinant PDE4 (the amount was controlled so that ~10% product was formed in 10min.). The reaction was stopped after 10min. by the addition of 1mg of PDE-SPA beads (Amersham Pharmacia Biotech, Inc., Piscataway, NJ). The product AMP generated was quantified on a Wallac Microbeta® 96-well plate counter (EG&G Wallac Co., Gaithersburg, MD). The signal in the absence of enzyme was defined as the background. 100% activity was defined as the signal detected in the presence of enzyme and DMSO with the background subtracted. Percentage of inhibition was calculated accordingly. IC₅₀ value was approximated with a non-linear regression fit using the standard 4-parameter/multiple binding sites equation from a ten point titration.

The IC₅₀ values of Examples 1-113 were determined with 100nM cAMP using the purified GST fusion protein of the human recombinant phosphodiesterase IVa (met-248) produced from a baculovirus/Sf-9 expression system. The IC₅₀ values of Examples 1-113 generally ranged from 0.1 nM to 25 nM.

The examples that follow are intended as an illustration of certain preferred embodiments of the invention and no limitation of the invention is implied.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. All operations were carried out at room or ambient temperature - that is, at a temperature in the range of 18-25°C. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000pascals: 4.5-30mm. Hg) with a bath temperature of up to 60°C. The course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only. Melting points are uncorrected and 'd' indicates

decomposition. The melting points given are those obtained for the materials prepared as described. Polymorphism may result in isolation of materials with different melting points in some preparations. The structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data. Yields are given for illustration only. When given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300MHz, 400MHz or 500MHz using the indicated solvent. Conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc. In addition, "Ar" signifies an aromatic signal. Chemical symbols have their usual meanings; the following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

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Methods of Synthesis

Compounds of the present invention can be prepared according to the following methods. The substituents are the same as in Formula I except where defined otherwise.

20

Scheme 1:

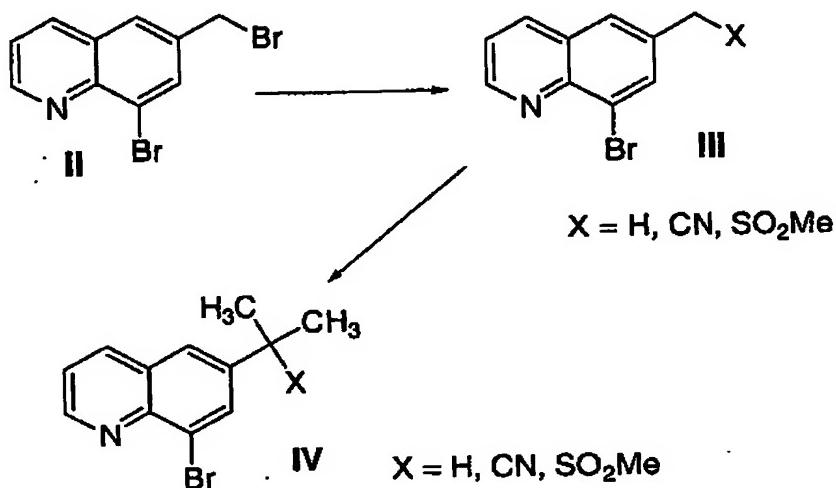
Preparation of 8-bromo-quinolines

The quinolines of formula IV may be obtained from literature procedure (R.H.F. Manske and M.Kulka, "The Skraup Synthesis of Quinolines"; Org. Reaction, vol. 7, p. 59-98, 1953 or in International Patent Publication WO 94/22852) or prepared in a multi-step sequence from the requisite 8-bromo-6-methyl-quinoline II. Treatment of 8-bromo-6-methyl-quinoline (from references cited in text) with brominating agents such as NBS in solvents such as chlorobenzene in presence of radical initiator such as AIBN or benzoyl peroxide provide the 8-bromo-6-bromomethyl-quinoline II. The primary bromide can be displaced by nucleophiles such as sodium methanesulfinate or potassium cyanide in a solvent such as DMF. Two sequential alkylation using alkylating agents such as iodomethane and a base

such as potassium t-butoxide in a solvent such as THF can yields 8-bromo-quinolines of such as IV.

Scheme 1

5



Scheme 2:
Preparation of 8-Aryl-quinolines

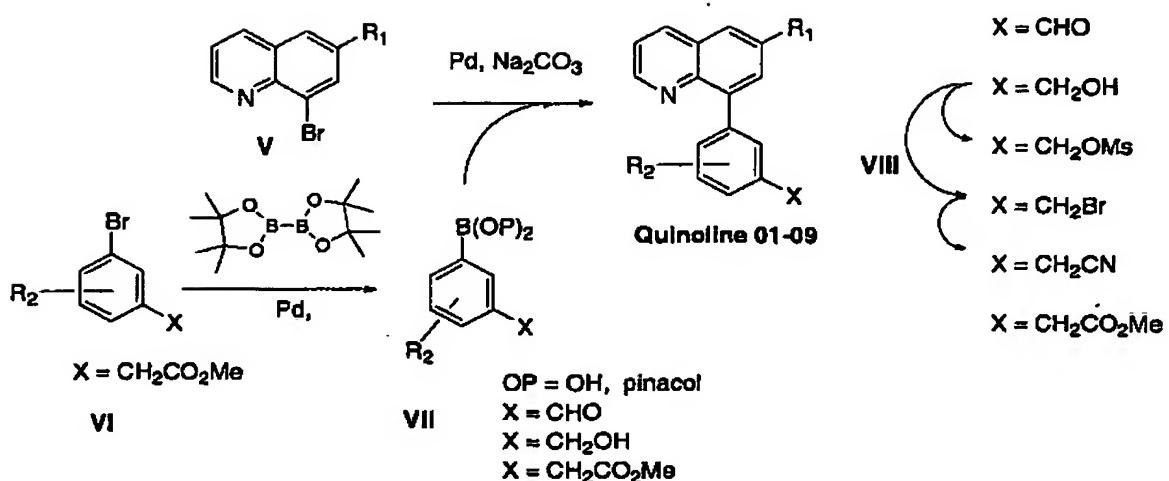
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The 8-aryl-quinolines of the formula VIII may be prepared by coupling the 8-bromo-quinoline such as V with appropriately substituted phenylboronic acids or esters such as VII with heating in the presence of various palladium catalyst such as $\text{Pd}(\text{Ph}_3\text{P})_4$ and a base such as sodium carbonate in a mixture of solvent such as DME-H₂O. The alcohol VIII ($X = \text{CH}_2\text{OH}$) may be converted to the bromide by treatment with HBr (aq.) in a solvent such as acetic acid or to the mesylate and then to the cyanide derivatives using standard organic chemistry protocols.

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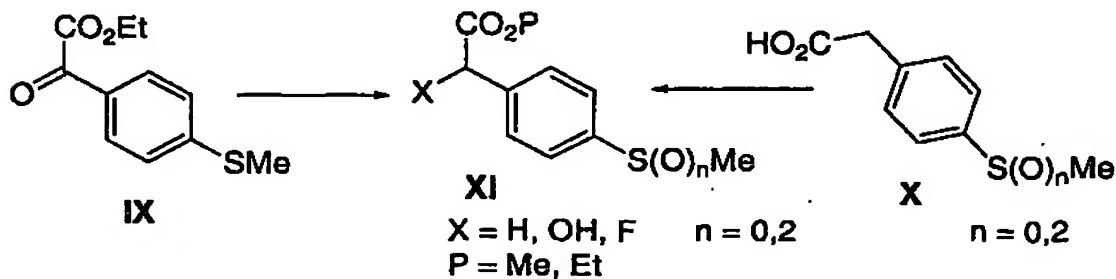
Scheme 2

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**Scheme 3:****5 Preparation of phenyl acetic acid derivatives**

The phenyl acetic acid derivatives XI may be prepared from esterification of commercial product such as X using diazomethane for example or by reduction of alpha-keto analog IX (*J. Med. Chem.*, **24**:399(1981)) using hydride such as NaBH₄ in a solvent such as ethanol. The alcohol XI (X = OH) can be transformed into XI (X = F) using DAST (*J. Org. Chem.*, **40**:574(1975)) or other commercial equivalents. Sulfur atom may also be oxidized to sulfone by oxidizing agent such as oxone in a mixture of solvents such as THF/MeOH/H₂O.

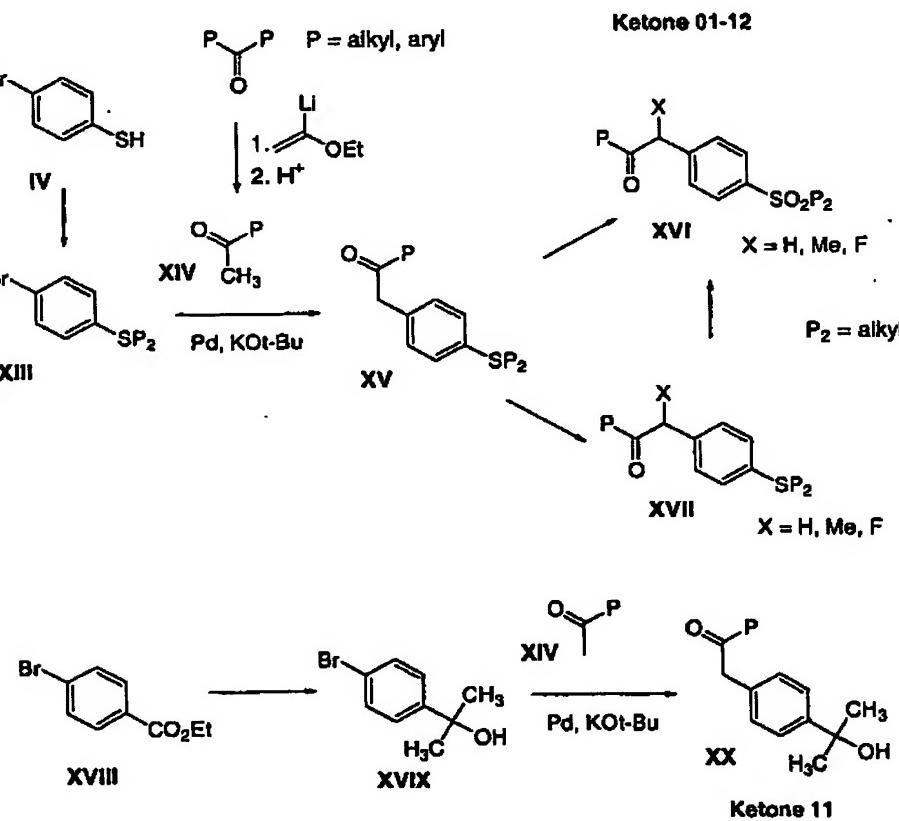
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Scheme 3**Ester 01-04**

Scheme 4:
Preparation of phenyl ethanone derivatives

Phenyl-ethanone intermediate like **XX** or **XV** may be prepared from 5 appropriately substituted aryl bromide and a methylketone using as a catalysis such as $\text{Pd}_2(\text{dba})_3$ with ligands such as xanphos or binap in a solvent like THF with a base such sodium tert-butoxide. Methyl ketone such as **XIV** can be obtained from commercial sources or prepared from condensation of ethyl vinyl ether lithium salt onto ketone such as 3-pentanone followed by hydrolysis in acidic media. Aryl 10 bromide such as **XIII** or **XVII** can be prepared using standard organic chemistry protocols. Further modifications of phenyl-ethanone such as **XV** will lead to substituted ethanone **XVI** and **XVII** by alkylation with alkyl iodide such as methyl iodide or a fluoride source such as N-fluorobzenesulfonimide (*Synlett*, 187, (1991)) and a base such as potassium tert-butoxide.

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Scheme 4

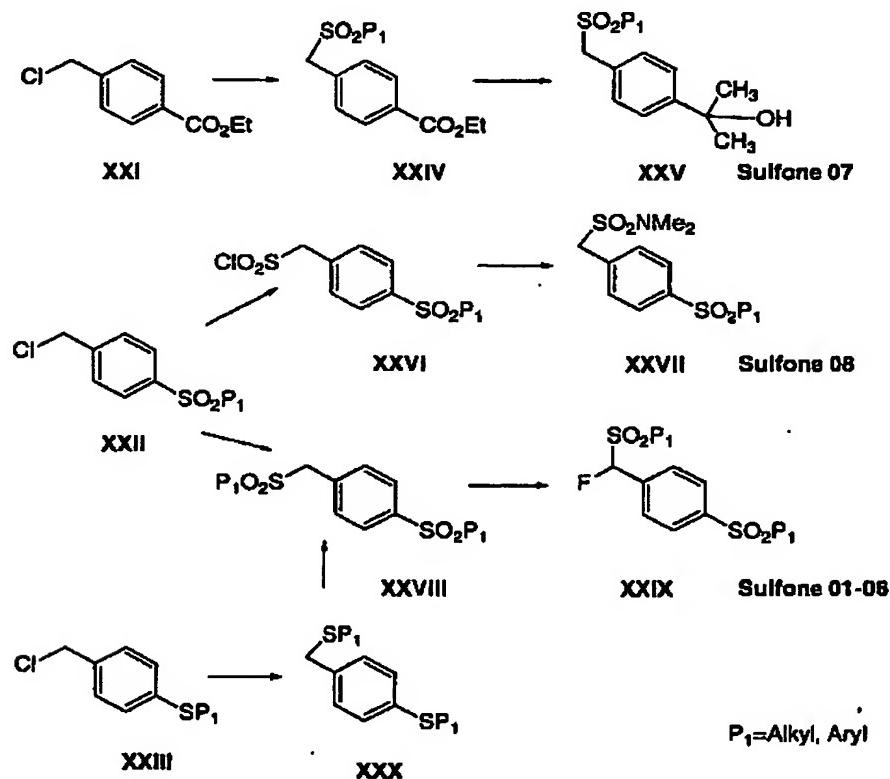
Scheme 5:
Preparation of sulfonylmethyl-phenyl derivatives

Sulfonylmethyl phenyl intermediate like **XXIV** to **XXX** may be prepared from appropriately substituted benzyl halide by displacement of halide by nucleophiles such as methanesulfonic acid sodium salt in a solvent such as DMF.

Alternatively, alkyl and aryl thiols can displace the benzylic halide with a base such as cesium carbonate in a solvent such as DMF. Oxidation of sulfide such as **XXX** with oxidizing agents such as oxone will lead to sulfone derivatives such as **XXVIII**.

Displacement of the benzylic halide with sulfur followed by oxidation with Cl_2 for example will afford the corresponding sulfonyl chloride such as **XXVI**. Further condensation with nucleophiles such as amines in a solvent like dichloromethane will give sulfonimides such as **XVII**. Those methylsulfone **XV** to **XVIII** can also be alkylated with a fluoride source such as N-fluorobenzenesulfonimide (*Synlett*, 187, (1991)) and a base such as potassium tert-butoxide to give alpha fluoro analogs such as **XXIX**.

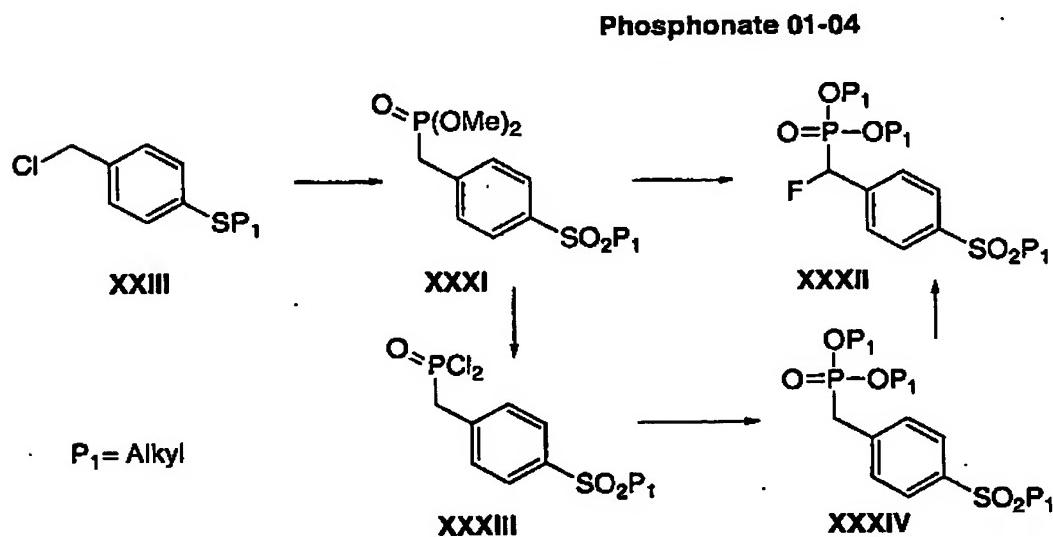
Scheme 5



Scheme 6:
Preparation of phosphonylmethyl-phenyl derivatives

5 Phosphonylmethyl phenyl intermediate like XXXI to XXXIV may be prepared from appropriately substituted benzyl halide by displacement of halide by nucleophiles such as trimethylphosphite. Hydrolysis to phosphonic acid may be accomplished using TMSBr in a solvent such as chloroform. Conversion to the acid chloride using oxalyl chloride for example in a solvent such as dichloromethane will
10 provide the starting material for further condensation with nucleophiles such as alcohol in a solvent like dichloromethane and with a base such as triethylamine to give various phosphonate esters such as XXXIV. The latter can also be alkylated with a fluoride source such as N-fluorobenzenesulfonimide (*Synlett*, 187, (1991)) and a base such as potassium tert-butoxide to give alpha fluoro analogs such as XXXII.

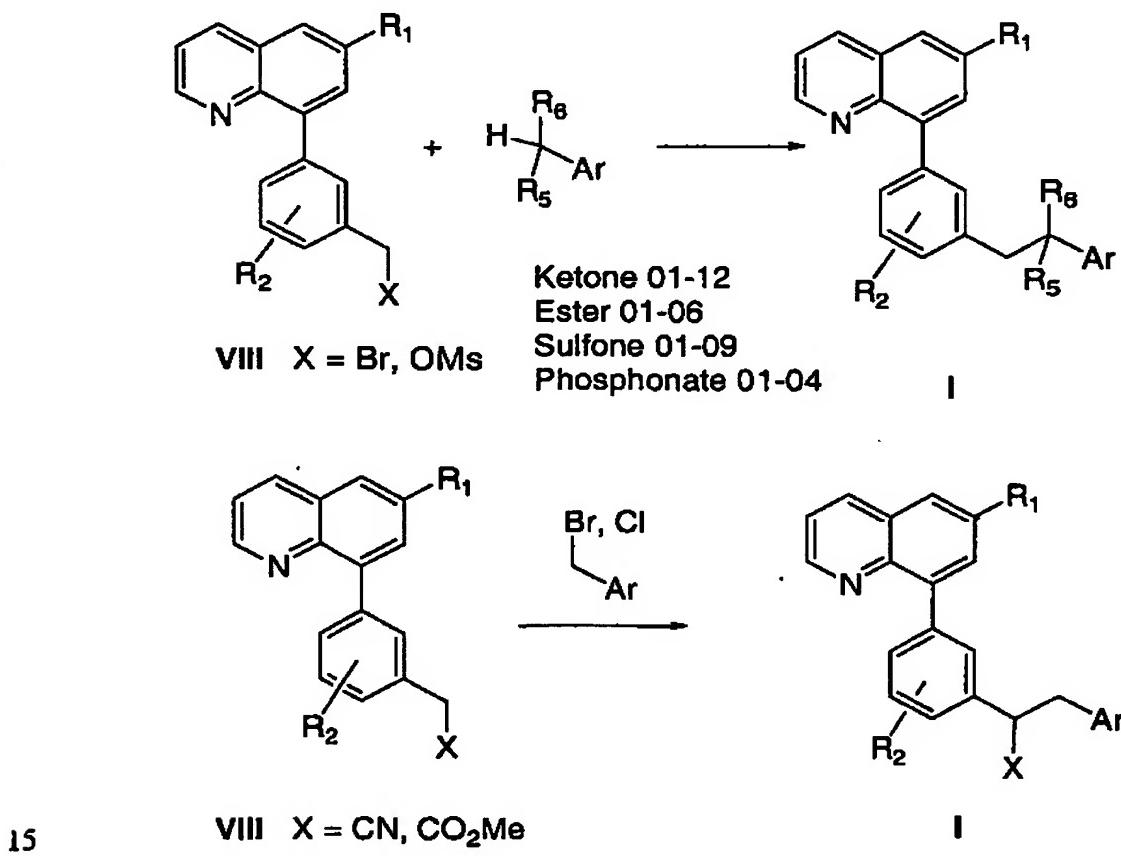
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Scheme 6

20 **Scheme 7:**
Preparation of quinoline of formula I

The quinolines of formula I may be obtained from alkylation of various carbonyl containing intermediates from Schemes 3 to 6 (esters, ketones, aldehydes, sulfonyl or phosphonates) with appropriate electrophile derivatives (Scheme 2). For example, the treatment of an intermediate (containing an acidic proton like a ketone etc..) with a base such as potassium t-butoxide in a organic solvent such THF, followed by quenching with an electrophile such as bromomethyl quinoline VIII, ($X=CH_2Br$) will give desired product of formula I. Alternatively, the quinoline / electrophile can be reverse to a quinoline / nucleophile and coupling with aryl halide will afford compounds with a different substitution pattern as described in Scheme 7.

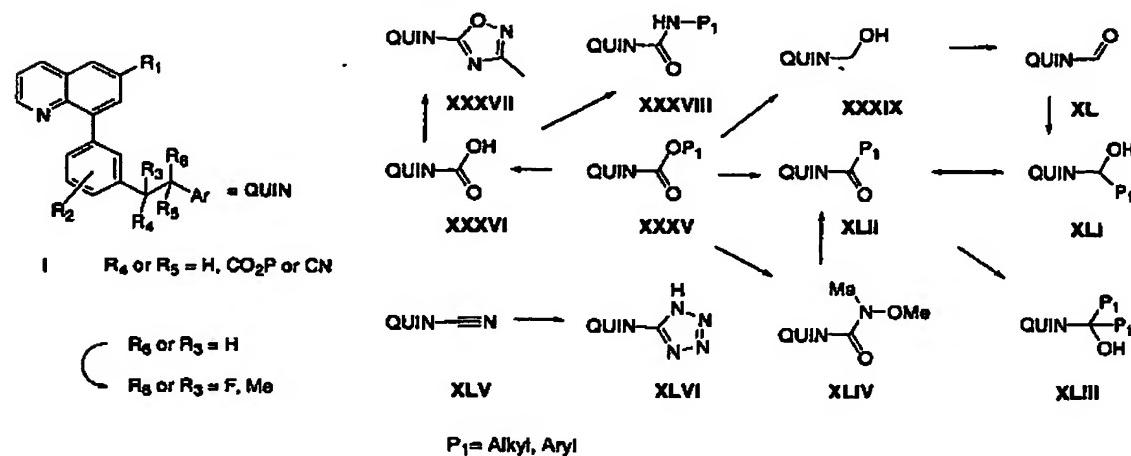
Scheme 7



Scheme 8:
Preparation of carboxylic acid derived analogs

5 Quinoline of formula I containing a carboxylic acid derivative such as XXXV can serve as a starting material for various other analogs as exemplified in Scheme 8. Formation of oxadiazole XXXVII may be achieved by activation of acetic acid XXXVI with EDCI in a solvent such as diglyme followed by the addition of N-hydroxy-acetamidine and subsequent heating of the reaction mixture. Formation of
10 the acid chloride or activation of acid by using standard procedures followed by addition of amines produces amide XXXVIII. Tetrazole like XXXXVI can be obtained from nitrile XXXV by heating with tributyltin azide in a solvent such as xylene. All other derivatives described in scheme 8 can be obtained using standard organic synthesis procedures related to reduction and addition of nucleophiles such as
15 lithium or magnesium salts to the carbonyl functional group. Those standards procedure also includes oxidation of alcohol to ketone and transformation of ester to Weinred type amide. All analogs containing a acidic proton at the benzoilic position, can also be alkylated with a fluoride source such as N-fluorobenzenesulfonimide
20 (Synlett, 187, (1991)) or alkyl halide such as methyl iodide and a base such as potassium tert-butoxide to give alpha fluoro analogs such as I (R₆ = F or Me).

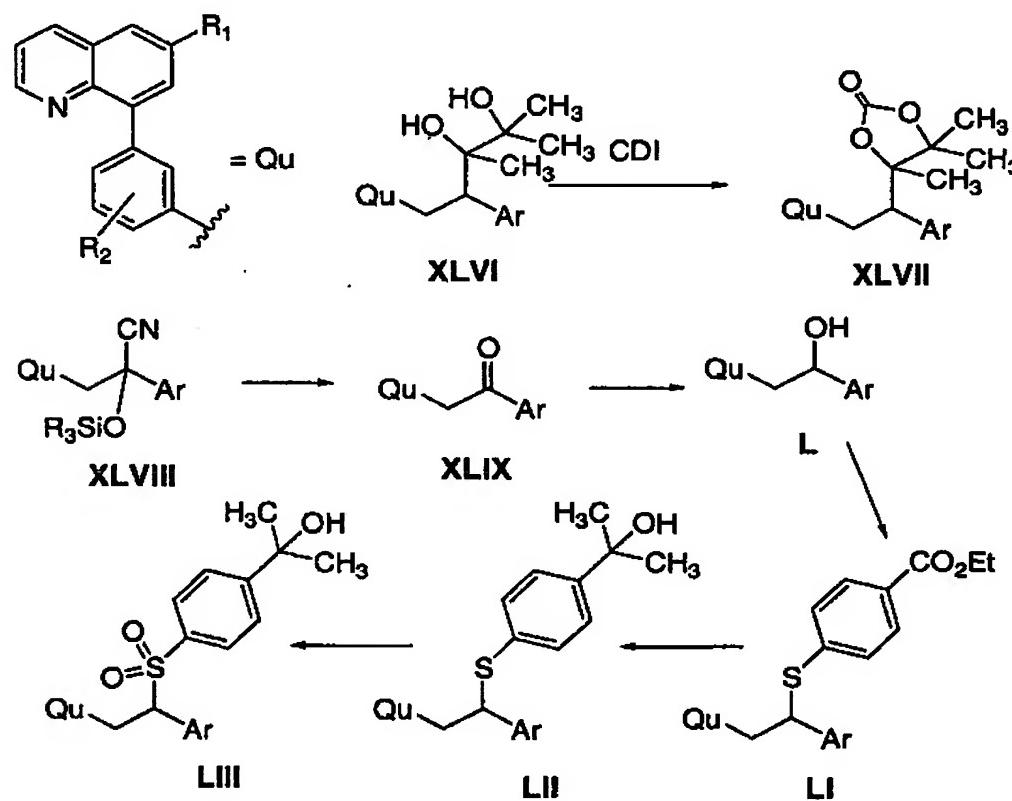
Scheme 8



Scheme 9:
Preparation of derivatives of quinoline of formula I

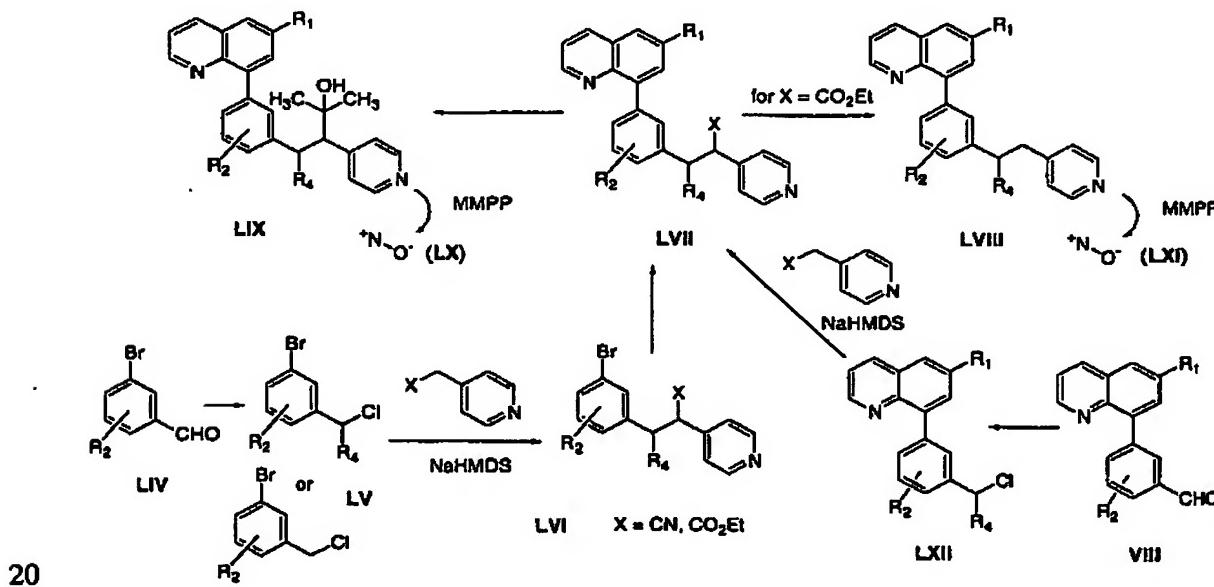
Alternatively, derivatives of formula I containing a masked carbonyl function in the form of a cyanohydrin of type **XLVIII** can be treated with tetra-butyl-
 5 ammonium fluoride in a solvent such as THF to give the ketone **XLIX**. Reduction of
 the carbonyl function with an hydride source such as sodium borohydride in a solvent
 such as methanol provides the secondary alcohol **L**. Mitsunubo type displacement of
 10 the benzylic alcohol with appropriate nucleophiles such as a substituted thiophenol
 will give the corresponding thio ether **LI**. Further manipulation of ester function to
 the tertiary alcohol and oxidation of sulfur to sulfone with an oxidizing agent such as
 oxone in a solvent such a mixture of THF/MeOH/H₂O gives **LIII**. 1,2-Diols like
XLVI can be cyclized to carbonate **XLVII** using, for example, carbonyl diimidazole
 and heating.

Scheme 9



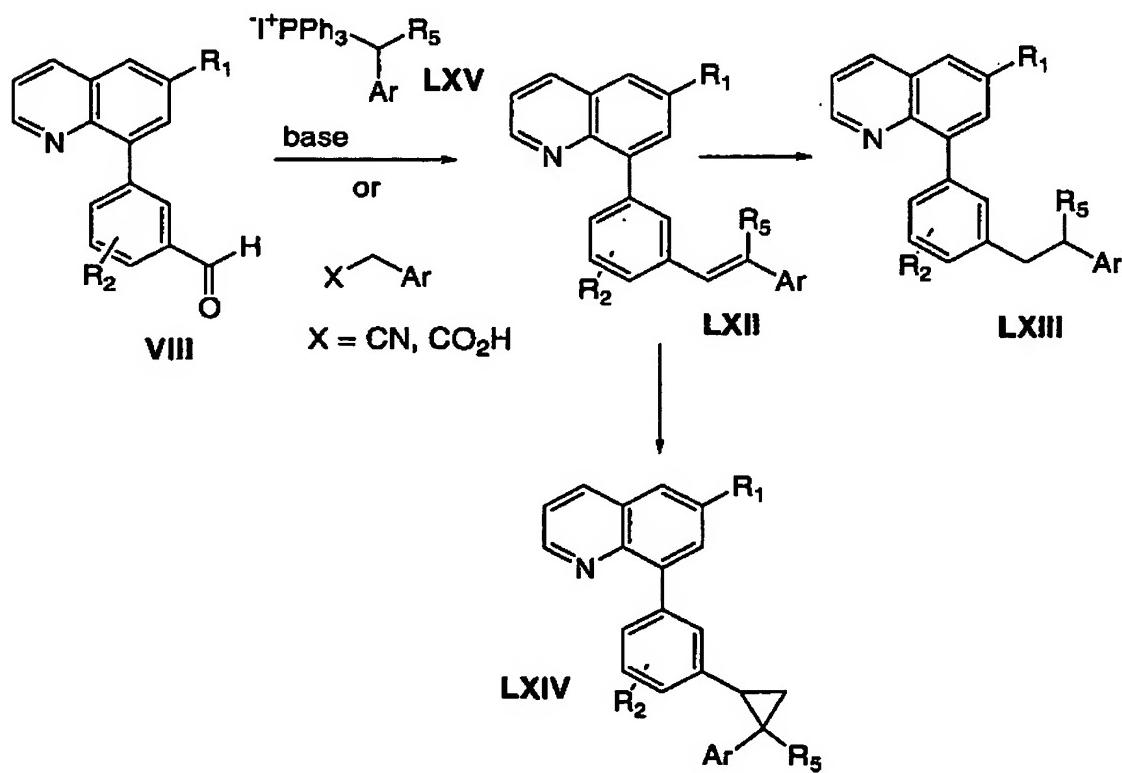
Scheme 10:**Preparation of 4-pyridinyl derivatives of quinoline of formula I**

Another synthetic approaches to quinoline of formula I is derived from custom made or commercial 3-bromobenzyl halides like LV. The latter can be derived from appropriately substituted benzaldehyde by addition of alkyl or arylmagnesium or lithium salts followed by conversion of the corresponding alcohol to the halide by using thionyl chloride, for example, in a solvent such as benzene. 4-Pyridinyl acetate or 4-pyridinyl acetonitrile can be deprotonated using a base such as NaHMDS and then alkylated with the benzylic halide LV or benzyl halide derived from quinoline VIII (Scheme 2). The derivatives of type LVII, with an ester functional group, can be hydrolyzed and decarboxylated to LVIII using an aqueous base such as NaOH followed by an acidic work-up. Alternatively, treatment of LVII with a nucleophile like methylmagnesium bromide for example, can produce tertiary alcohol like LIX. Other functional group manipulation from an ester was described in Scheme 8. The pyridinyl can be oxidized to the pyridinyl N-oxide with an oxidizing agent such as MMPP in a solvent such a mixture of CH₂Cl₂/MeOH to gives LX or LXI.

Scheme 10

Scheme 11:
Preparation of stilbene derivatives of quinoline of formula I

- 5 Intermediate such as **LXII** - containing a double bond can serve as a precursor to compound of formula **I**. Condensation of aldehydes **VIII** with substituted acetic acid or acetonitrile and a base such as piperidine and heating will provide **LXII**. Alternatively, phosphonium salts **LXV** with a base such as potassium tert-butoxide in a solvent such as THF can react with aldehyde of formula **VIII**.
- 10 Reduction of the olefin using catalyst such as palladium on carbon in a solvent such as THF/MeOH under hydrogen atmosphere or polymer supported phenylhydrazide in a solvent such as toluene with heating will provide compound like **LXIII**. Cyclopropanation of the double bond using trimethyl-sulfoxonium iodide and a base such as NaH in a solvent such as DMSO will give derivatives of formula **LXIV**.
- 15 **Scheme 11**



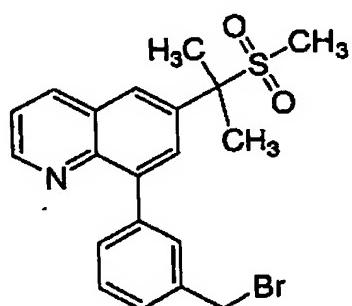
PREPARATION OF INTERMEDIATES

5

PREPARATION OF QUINOLINES

Quinoline 01

8-(3-Bromomethyl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



10

Step 1: 8-Bromo-6-methanesulfonylmethyl-quinoline

To a solution of 6-bromomethyl-8-bromoquinoline (60g, 200mmol, described in International Patent Publication WO 94/22852) in DMF (500mL) was 15 added sodium methanesulfinate (27.6g, 270mmol). After stirring overnight at 21°C, the mixture was quenched with H₂O (2L), stirred for 1h, isolated by filtration, and washed with Et₂O to yield the 8-Bromo-6-methanesulfonylmethyl-quinoline as a white solid.

20 Step 2: 8-Bromo-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

To a solution of the 8-Bromo-6-methanesulfonylmethyl-quinoline from Step 1 above (60g, 200mmol) in THF (2L) at 0°C (internal), was added potassium *t*-butoxide (260mL, 1M, THF) over 30min. After 0.5h at 0°C, MeI (20mL, 320mmol) was added and the resulting reaction mixture stirred at 0°C for 2h. More potassium *t*-butoxide (200mL, 1M, THF) was then added over 30min, followed by MeI (20mL, 320mmol), and the mixture stirred at rt for 2h. The mixture was neutralised with saturated NH₄Cl solution and extracted with EtOAc. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Stirring the solid in ether, followed by filtration gave the 8-Bromo-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline as a pale yellow solid.

Step 3: {3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol

A mixture of the 8-Bromo-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from Step 2 above (26g, 79mmol), 3-(hydroxymethyl) phenyl-boronic acid (14g, 92mmol), sodium carbonate (120mL, 2M, H₂O), PdCl₂(Ph₃P)₂ (2g) in DME (300mL) was heated at 90-100°C for 8h. The resulting reaction mixture was filtered on a large plug/column of silica gel and the eluted with EtOAc. The organic extracts were concentrated and the resulting suspension diluted with Et₂O and stirred vigorously for 3h. The desired {3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol was isolated as a white solid by filtration.

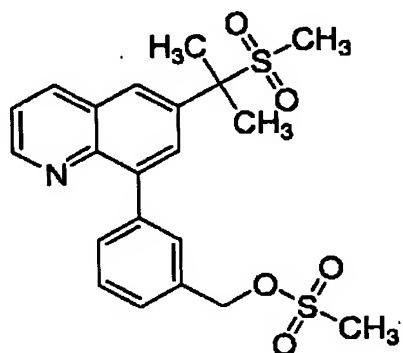
Step 4: 8-(3-Bromomethyl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

A suspension of the {3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol compound from Step 3 above (30g, 85mmol) in AcOH (140mL) and HBr (48mL, 48% aq) was stirred for 18h at 80°C. The resulting mixture was cooled to 0°C and poured into 2L of cold NaOH (0.3N). The pH of the resulting solution was adjusted to 5 and filtered. The resulting solid was dissolved in EtOAc, washed with saturated NaHCO₃ solution, brine, dried (MgSO₄), filtered and concentrated. Stirring the solid in ether/ EtOAc, followed by filtration gave desired

8-(3-Bromomethyl-phenyl)-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline as a pale brown solid.

Quinoline 02

5 {3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-methanol O-methanesulfonate

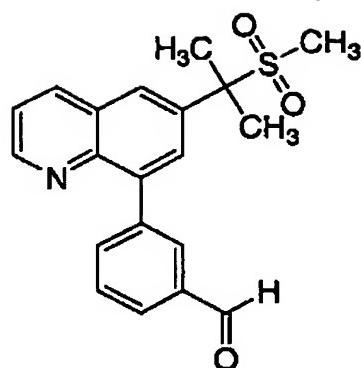


To a solution of the alcohol from Quinoline 01, Step 3 (5.15g, 17mmol) in CH₂Cl₂ (150mL) at -78°C was added Et₃N (3.6mL, 26mmol) and methanesulfonyl chloride (1.6mL, 21mmol). After 0.5h at -78°C, the mixture was neutralized with saturated NH₄Cl solution, diluted with water, and extracted with ether. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered, and concentrated to yield the title compound as a white foam.

15

Quinoline 03

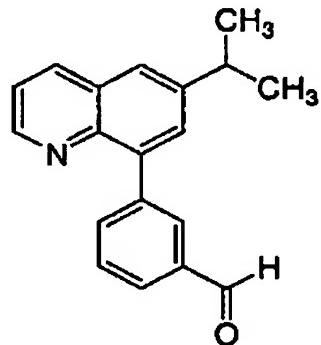
3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-benzaldehyde



Following the procedures described in **Quinoline 01, Steps 1-3**, but substituting 3-formylphenyl-boronic acid for 3-(hydroxymethyl)-phenyl-boronic acid in **Step 3**, the title compound was obtained as pale yellow solid.

5

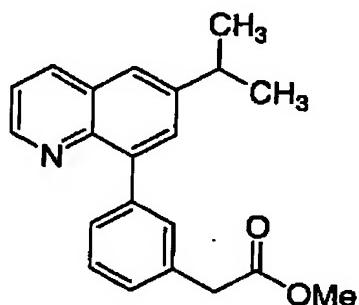
Quinoline 04
3-(6-Isopropyl-quinolin-8-yl)-benzaldehyde



- A mixture of 8-bromo-6-isopropyl-quinoline (9.79g, 39mmol),
10 described in International Patent Publication WO 94/22852), 3-(formyl)-phenyl-
boronic acid (11.7g, 78mmol), sodium carbonate (78mL, 2M, H₂O), Pd(PPh₃)₄ (2.7g,
2.3mmol) in DME (200mL) was heated at 70°C for 18h. The reaction mixture was
cooled to 21°C then diluted with water and ethyl acetate. The organic extracts were
washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash
15 chromatography (eluting with hexane/ethyl acetate, 80:20) provided the title
compound.

Quinoline 05

[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetic acid methyl ester

**Step 1: (3-Bromo-phenyl)-acetic acid methyl ester**

5 To a solution of 3-bromophenylacetic acid (10g, 46mmol) in CH₂Cl₂ (20mL) was added CH₂N₂ (Et₂O) until yellow coloration persisted. The resulting reaction mixture was quenched with AcOH, and diluted with a NaHCO₃ solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated to provided the (3-Bromo-phenyl)-acetic acid methyl ester compound.

10

Step 2: [3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester

A solution of (3-Bromo-phenyl)-acetic acid methyl ester from Step 1 (10.9mg, 48mmol), diboron pinacol ester (14.5g, 57mmol), KOAc (16.33g, 166mmol) and PdCl₂(dppf) (1.94g, 2.38mmol) in DMF (250mL) was heated at 80°C under N₂ for 3h. The resulting reaction mixture was cooled to 21°C and diluted with water and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 65:35) provided the [3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester compound.

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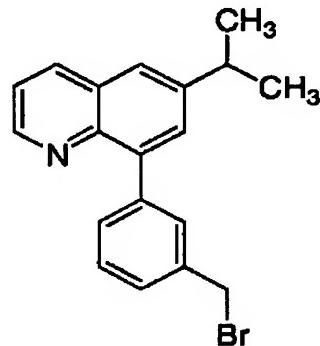
20

Step 3: [3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetic acid methyl ester

A solution of [3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-acetic acid methyl ester from Step 2 (4g, 14mmol), 8-bromo-6-isopropylquinoline (3g, 12mmol), Na₂CO₃ (2M, 18mL, 36mmol) and Pd(PPh₃)₄ (692mg, 0.6mmol) in DMF (250mL) was heated at 80°C under N₂ for 18h. The 5 resulting reaction mixture was cooled to 21°C and diluted with water and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20) provided the [3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetic acid methyl ester compound.

10

Quinoline 06
8-(3-Bromomethyl-phenyl)-6-isopropyl-quinoline



Quinoline 06 was prepared according to the procedure described in
15 Quinoline 01, Steps 3 and 4, but 6-isopropyl-8-bromo-quinoline was used as the starting material. Flash chromatography (hexane/EtOAc) afforded the title compound as a yellow solid.

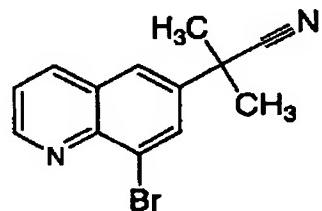
20 **Quinoline 07**
[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-acetonitrile



To a solution of **Quinoline 06** (1.0g, 2.94mmol) in CH₃CN (15mL) was added KCN (244mg, 3.74mmol) and 18-crown-6 (100mg, 0.37mmol). The resulting reaction mixture was stirred 18h at 80°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 75:25) provided the title compound.

10

Quinoline 08
2-(8-Bromo-quinolin-6-yl)-2-methyl-propionitrile



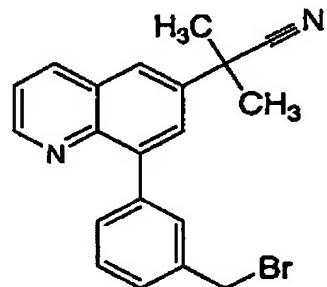
Step 1: (8-Bromo-quinolin-6-yl)-acetonitrile

DMF (10mL) and H₂O (5mL) were added to 6-bromomethyl-8-bromoquinoline (3g) (described in International Patent Publication WO 94/22852) and potassium cyanide (1.6g). After heating at 100°C for 1 hour, the resulting mixture was quenched with H₂O (100mL) and extracted with EtOAc. The combined organic extracts were washed with water (3x), brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (hexane:EtOAc, 3:1) yielded the (8-Bromo-quinolin-6-yl)-acetonitrile compound as a white solid.

Step 2: 2-(8-Bromo-quinolin-6-yl)-2-methyl-propionitrile

To a solution of (8-Bromo-quinolin-6-yl)-acetonitrile from Step 1 (3g, 12.1mmol) in THF (100mL) at -78°C, was added MeI (1.7mL, 27mmol) followed by 5 potassium *t*-butoxide (27mL, 27mmol). After 2h at -78°C, the resulting mixture was warmed to 0°C, was poured in saturated aqueous NH₄Cl, then extracted with EtOAc (2x). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated. Flash chromatography (hexane:EtOAc, 3:1) afforded the 2-(8-Bromo-quinolin-6-yl)-2-methyl-propionitrile as a white solid.

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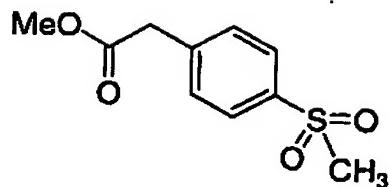
Quinoline 09**2-[8-(3-Bromomethyl-phenyl)-quinolin-6-yl]-2-methyl-propionitrile**

Quinoline 09 was prepared according to the procedure described 15 above in Quinoline 01, Steps 3 and 4 but used Quinoline 08 as the starting material. Flash chromatography (hexane/EtOAc) afforded the title compound as a yellow solid.

PREPARATIONS OF ESTERS

20

Ester 01**(4-Methanesulfonyl-phenyl)-acetic acid methyl ester**

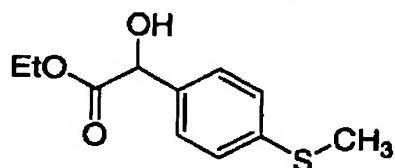


(4-Methanesulfonyl-phenyl)-acetic acid was treated with an ethereal solution of diazomethane until completion of esterification by TLC. The solvent was evaporated, the residue triturated in hexane/ether and filtered to afford the title compound as a white solid.

5

Ester 02

Hydroxy-(4-methylsulfanyl-phenyl)-acetic acid ethyl ester



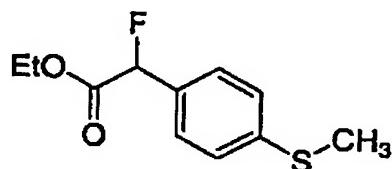
To a solution of ethyl α -oxo 4-methylthiophenylacetate (obtained from thioanisole and ethyl oxalyl chloride using procedure described in *J. Med. Chem.*, p.403(1981) (30g, 134mmol) in EtOH at -78°C, was added NaBH₄ (2.5g, 66mmol) portionwise. After 40min at -78°C, the resulting reaction mixture was quenched by slow addition of a saturated ammonium chloride solution, allowed to warm to 21°C, poured into water (0.5L) and stirred for 2h. The suspension was filtered to provide the title compound as a white solid.

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15

Ester 03

Fluoro-(4-methylsulfanyl-phenyl)-acetic acid ethyl ester



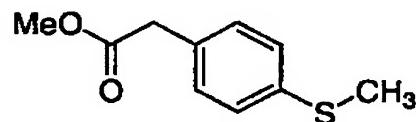
20

To a solution of Ester 02 (10.9g, 48mmol) in CH₂Cl₂ (300mL) at 78°C was added [bis(2-methoxyethyl)amino]sulfur trifluoride (10mL, 54mmol) dropwise. The resulting reaction mixture was warmed slowly to 10°C, then poured into an ether/NaHCO₃ solution. The organic extracts were washed (H₂O), (brine), 5 dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 95:5) provided the title compound as an oil.

Ester 04

(4-Methylsulfanyl-phenyl)-acetic acid methyl ester

10

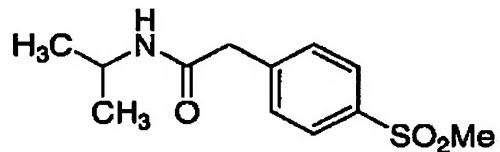


(4-Methylsulfanyl-phenyl)-acetic acid was treated with an ethereal solution of diazomethane until completion of esterification. The solvent was evaporated, the residue triturated in hexane/ether, and filtered to afford the title compound as a white solid.

15

Ester 05

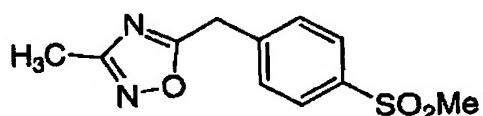
N-Isopropyl-2-(4-methanesulfonyl-phenyl)-acetamide



To a solution of (4-methanesulfonyl-phenyl)-acetic acid (2.5g, 11.7mmol) in CH₂Cl₂ (20mL) was added EDCI (2.46g, 12.9mmol) followed by diisopropyl amine (1.2mL) and DMAP (140mg, 1.2mmol). After 18h at 21°C, the resulting reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate/THF, 35:60:5) provided the title compound as a white solid.

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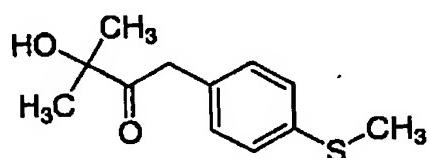
Ester 06**5-(4-Methanesulfonyl-benzyl)-3-methyl-[1,2,4]oxadiazole**

Ester 06 prepared according to the procedure described in Example 83 but using (4-methanesulfonyl-phenyl)-acetic acid as the starting material. Flash chromatography (hexane/EtOAc) afforded the title compound as a yellow solid.

15

PREPARATION OF KETONES

20

Ketone 01**3-Hydroxy-3-methyl-1-(4-methylsulfanyl-phenyl)-butan-2-one**

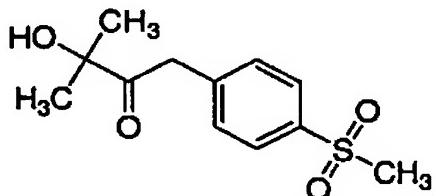
To a solution of sodium *tert*-butoxide (12g, 125mmol), XANTPHOS (2.05g, 3.5mmol) and Pd₂(dba)₃ (1.35g, 1.5mmol) in THF (600mL) was added 4-bromothioanisole (20g, 98mmol) and 3-hydroxy-3-methyl-butan-2-one (12g,

25

117mmol). The resulting reaction mixture was heated to 75°C for 2h then cooled to r.t. and diluted with water. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 85:15-80:20) provided the title compound as a pale brown
5 solid.

Ketone 02

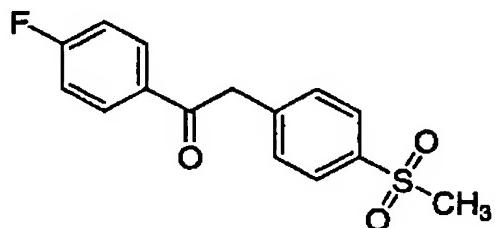
3-Hydroxy-1-(4-methanesulfonyl-phenyl)-3-methyl-butan-2-one



10 To a solution of **Ketone 01** (10.7g, 48mmol) in THF/MeOH (2:1, 375mL) was added OXONE® (60g, 98mmol) followed by water (slowly, 125mL). After 2h, the reaction mixture was diluted with ether and a saturated NaHCO₃ solution. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by stirring vigorously in hexane/ether and isolation by
15 filtration gave the desired product as a pale yellow solid (8.3g).

Ketone 03

1-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-ethanone



20 **Step 1:** 1-(4-Fluoro-phenyl)-2-(4-methylsulfanyl-phenyl)-ethanone

To a solution of sodium *tert*-butoxide (480mg, 5mmol), BINAP (racemic, 112mg, 0.18mmol) and Pd₂(dba)₃ (68mg, 0.075mmol) in THF (10mL) was

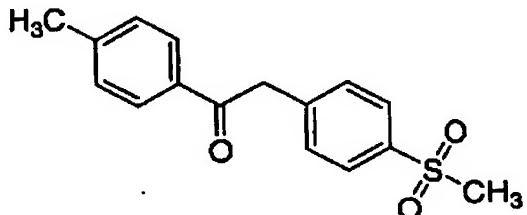
added 4-bromo-thioanisole (914mg, 4.5mmol) and 4-fluoro-acetophenone (690mg, 5mmol). The resulting reaction mixture was heated to 80°C for 3h then cooled to 21°C and diluted with water. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 8:2) provided the 1-(4-Fluoro-phenyl)-2-(4-methylsulfanyl-phenyl)-ethanone compound as a solid after precipitation in ether/ethyl acetate.

Step 2: 1-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-ethanone

Following the procedures described in **Ketone 02** but substituting 1-(4-fluoro-phenyl)-2-(4-methylsulfanyl-phenyl)-ethanone for **Ketone 01**, the 1-(4-fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-ethanone compound was obtained as a white solid.

Ketone 04

15 **2-(4-Methanesulfonyl-phenyl)-1-p-tolyl-ethanone**

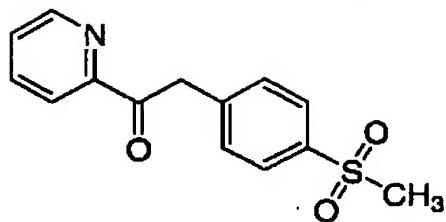


Following the procedures described in **Ketone 03**, but substituting 4-methyl-acetophenone for 4-fluoro-acetophenone, the title compound was obtained as a white solid.

20

Ketone 05

2-(4-Methanesulfonyl-phenyl)-1-pyridin-2-yl-ethanone

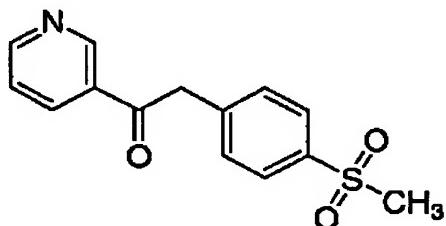


Following the procedures described in **Ketone 03**, but substituting 2-acetylpyridine for 4-fluoroacetophenone, the title compound was obtained as a beige solid.

5

Ketone 06

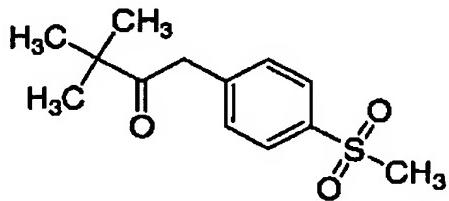
2-(4-Methanesulfonyl-phenyl)-1-pyridin-3-yl-ethanone



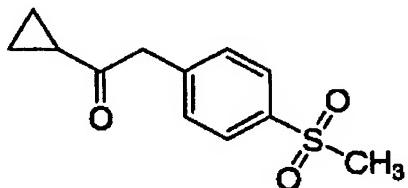
Following the procedures described in **Ketone 03**, but substituting 3-acetyl-pyridine for 4-fluoro-acetophenone, the title compound was obtained.

Ketone 07

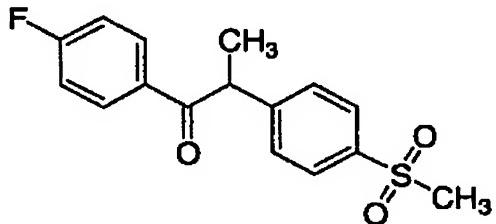
1-(4-Methanesulfonyl-phenyl)-3,3-dimethyl-butan-2-one



15 Following the procedures described in **Ketone 03**, but substituting pinacolone for 4-fluoroacetophenone, the title compound was obtained as a white solid.

Ketone 08**1-Cyclopropyl-2-(4-methanesulfonyl-phenyl)-ethanone**

Following the procedures described in **Ketone 01** and **Ketone 02**, but
 5 substituting 1-cyclopropyl-ethanone for 3-hydroxy-3-methyl-butan-2-one, the title compound was obtained.

Ketone 09**1-(4-Fluoro-phenyl)-2-(4-methanesulfonyl-phenyl)-propan-1-one**

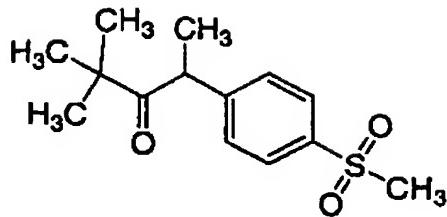
10

To a solution of **Ketone 03** (240mg, 0.822mmol) in THF (8mL) at -30°C was added potassium tert-butoxide (1M, THF, 0.9mL, 0.9mmol) dropwise. After 20min, iodomethane (0.076mL, 1.22mmol) was added and the resulting reaction mixture was stirred for 2h at -20°C, and then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 95:5) provided the title compound.
 15

Ketone 10

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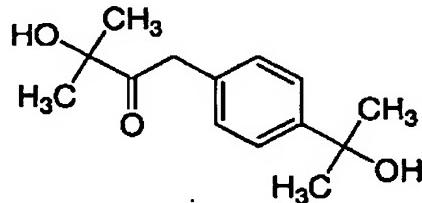
4-(4-Methanesulfonyl-phenyl)-2,2-dimethyl-pentan-3-one



Following the procedures described in **Ketone 01**, but substituting pinacolone for 3-hydroxy-3-methyl-butan-2-one, followed by the procedures described in **Ketone 09** and finally using procedures described in **Ketone 02**, the title compound was obtained.

Ketone 11

3-Hydroxy-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-methyl-butan-2-one



10 **Step 1: 2-(4-Bromo-phenyl)-propan-2-ol**

Following the procedures described in **Example 24**, but substituting ethyl 4-bromobenzoate for **Example 07**, the 2-(4-bromo-phenyl)-propan-2-ol compound was obtained as a white solid.

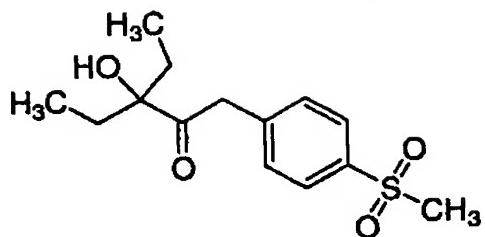
15 **Step 2: 3-Hydroxy-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-methyl-butan-2-one**

Following the procedures described in **Ketone 01**, but substituting 2-(4-bromophenyl)-2-propanol for 4-bromothioanisole, the 3-hydroxy-1-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-3-methyl-butan-2-one compound was obtained as an oil.

20

Ketone 12

3-Ethyl-3-hydroxy-1-(4-methanesulfonyl-phenyl)-pentan-2-one

**Step 1: 3-Ethyl-3-hydroxy-pentan-2-one**

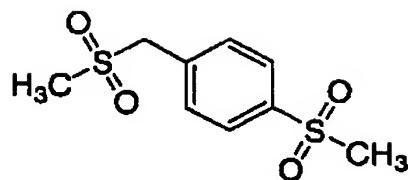
To a solution of ethyl vinyl ether (10mL, 104mmol) in THF (50mL) at -78°C was added tert-BuLi (1.7M, pentane, 45mL, 76mmol) dropwise. The mixture was stirred at -10°C for 15min then cooled to -78°C and 3-pentanone (5.0g, 58mmol, in 5mL of THF) was added dropwise. The resulting reaction mixture was allowed to warm slowly to 21°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extract was stirred with 6mL of HCl 2% for 18h then washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. The residue was purified by flash chromatography (eluting with hexane/ethyl acetate, 95:5) to provide the 3-ethyl-3-hydroxy-pentan-2-one compound as an oil.

Step 2: 3-Ethyl-3-hydroxy-1-(4-methanesulfonyl-phenyl)-pentan-2-one

Following the procedures described in Ketone 01 then in Ketone 02, 15 but substituting 3-ethyl-3-hydroxy-pentan-2-one for 3-hydroxy-3-methyl-butan-2-one. Purification by flash chromatography (eluting with ethyl acetate/hexane, 3:2) afforded the 3-ethyl-3-hydroxy-1-(4-methanesulfonyl-phenyl)-pentan-2-one compound as a white foam.

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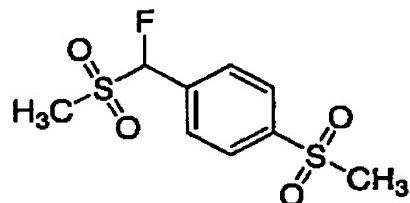
PREPARATION OF SULFONES**Sulfone 01****1-Methanesulfonyl-4-methanesulfonylmethyl-benzene**



To a solution of 4-methanesulfonylbenzyl chloride (2g, 10mmol) in DMF (20mL) at 21°C was added sodium methanesulfinate (1.5g, 15mmol). After 18h, the mixture is poured into cold water (100mL), stirred for 30min then filtered off 5 to afford the title compound as a white solid.

Sulfone 02

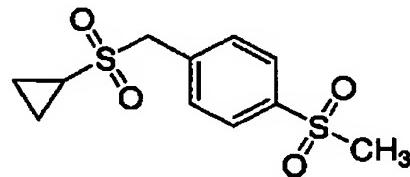
1-(Fluoro-methanesulfonyl-methyl)-4-methanesulfonyl-benzene



To a solution of Sulfone 01 (275mg, 1.1mmol) in DMF (6mL) at 0°C 10 was added potassium tert-butoxide (1M THF, 1.5mL, 1.5mmol) followed, after 10min, by N-fluorobenzenesulfonyl imide (419mg, 1.3mmol). The reaction mixture was diluted with a saturated sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and 15 concentrated. Purification by flash chromatography (eluting with CH₂Cl₂/acetone, 97:3) provided the title compound.

Sulfone 03

1-Cyclopropanesulfonylmethyl-4-methanesulfonyl-benzene



20

Step 1: (4-Methylsulfanyl-phenyl)-methanethiol disulfide

A solution of sulfur (1g, 29mmol) in benzene (60mL), PEG 400 (1 drop) and NaOH (5N, 46mL, 232mmol) was heated at 65°C for 3h. 4-methylthiobenzyl chloride (4g, 23mmol) and a catalytic amount of 5 tetrabutylammonium iodide was added and the mixture stirred at 65°C for 2h. The reaction was cooled at 21°C and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. The residue was stirred vigorously in ethanol/ether for 1h then filtered to afford the (4-methylsulfanyl-phenyl)-methanethiol disulfide compound 10 as a pale rose powder.

Step 2: 1-Cyclopropylsulfanylmethyl-4-methylsulfanyl-benzene

To a solution of (4-methylsulfanyl-phenyl)-methanethiol disulfide from Step 1 in THF (50mL) at 21°C was added cyclopropylmagnesium bromide (excess) 15 dropwise. The reaction mixture was stirred 18h at 21°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 98:2) provided the 1-cyclopropylsulfanylmethyl-4-methylsulfanyl-benzene compound as an oil.

20

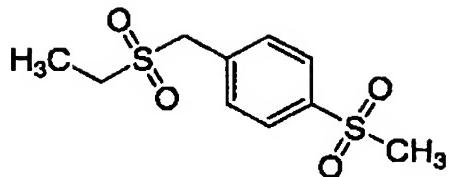
Step 3: 1-Cyclopropanesulfonylmethyl-4-methanesulfonyl-benzene

Following the procedures described in Example 16, but substituting 1-cyclopropylsulfanylmethyl-4-methylsulfanyl-benzene thioether from Step 2 for Example 15 and purification by flash chromatography (eluting with hexane/ethyl 25 acetate, 50:50 to 0:100) provided the 1-cyclopropanesulfonylmethyl-4-methanesulfonyl-benzene compound as a solid.

Sulfone 04

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1-Ethanesulfonylmethyl-4-methanesulfonyl-benzene



Step 1: 1-Ethylsulfanylmethyl-4-methanesulfonyl-benzene

To a solution of ethanethiol (0.3mL, 4.9mmol) and 4-methanesulfonylbenzyl chloride (1g, 4.9mmol) in DMF (10mL) at 21°C was added 5 cesium carbonate (0.8g, 2.5mmol). After 18h, the reaction mixture was poured into water and then filtered off to provide the 1-ethylsulfanylmethyl-4-methanesulfonyl-benzene compound as a white solid.

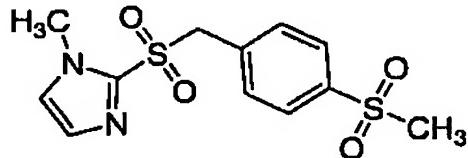
Step 2: 1-Ethanesulfanylmethyl-4-methanesulfonyl-benzene

10 Following the procedures described in Example 16, but substituting the 1-ethylsulfanylmethyl-4-methanesulfonyl-benzene thioether from Step 1 for Example 15, the 1-ethanesulfanylmethyl-4-methanesulfonyl-benzene compound was isolated as a white solid.

15

Sulfone 05

2-(4-Methanesulfonyl-phenylmethanesulfonyl)-1-methyl-1H-imidazole

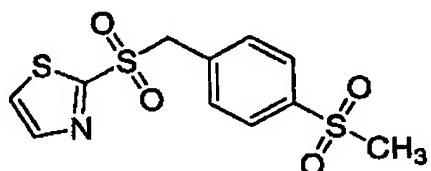


Step 1: 2-(4-Methanesulfonyl-benzylsulfanyl)-1-methyl-1H-imidazole

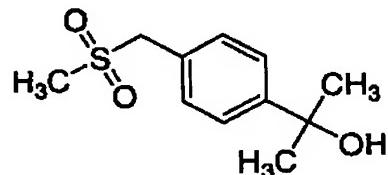
20 To a solution of 2-mercapto-N-methylimidazole (570mg, 4.9mmol) and 4-methanesulfonylbenzyl chloride (1g, 4.9mmol) in DMF (10mL) at 21°C was added cesium carbonate (0.8g, 2.5mmol). After 18h, the reaction mixture was diluted with water and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated to provide the 2-(4-methanesulfonyl-benzylsulfanyl)-1-methyl-1H-imidazole compound as a white solid.

Step 2: 2-(4-Methanesulfonyl-phenylmethanesulfonyl)-1-methyl-1H-imidazole

Following the procedures described in **Example 16**, but substituting the 2-(4-methanesulfonyl-benzylsulfanyl)-1-methyl-1H-imidazole thioether from **Step 1** for **Example 15**, the 2-(4-methanesulfonyl-phenylmethanesulfonyl)-1-methyl-1H-imidazole compound was isolated as a white solid.

Sulfone 06**2-(4-Methanesulfonyl-phenylmethanesulfonyl)-thiazole**

Following the procedures described in **Sulfone 04**, but substituting 2-mercaptopthiazole for ethanethiol, the title compound was obtained as a white solid.

Sulfone 07**2-(4-Methanesulfonylmethyl-phenyl)-propan-2-ol****Step 1: 4-Methanesulfonylmethyl-benzoic acid methyl ester**

Following the procedures described in **Sulfone 01**, but substituting 4-carboxymethylbenzyl chloride for 4-methanesulfonylbenzyl chloride, the 4-methanesulfonylmethyl-benzoic acid methyl ester compound was obtained as a white solid.

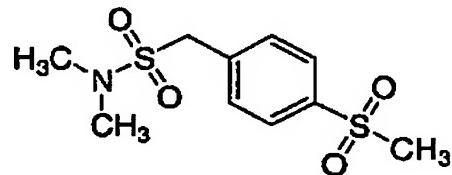
Step 2: 2-(4-Methanesulfonylmethyl-phenyl)-propan-2-ol

Following the procedures described in Example 29, but substituting the 4-methanesulfonylmethyl-benzoic acid methyl ester from Step 1 for Example 27, the 2-(4-methanesulfonylmethyl-phenyl)-propan-2-ol compound was obtained as a white solid.

5

Sulfone 08

C-(4-Methanesulfonyl-phenyl)-N,N-dimethyl-methanesulfonamide



Step 1: (4-Methanesulfonyl-phenyl)-methanethiol

- 10 To a solution of potassium acetate (5.86g, 51mmol) in THF/DMF (3:1, 400mL) was added 4-methanesulfonylbenzyl chloride (10g, 49mmol). After 3h at 21°C, the resulting reaction mixture was quenched with LiOH (1M) and stirred again for 2h. The mixture was diluted with HCl 10% solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with CH₂Cl₂) provided the (4-methanesulfonyl-phenyl)-methanethiol compound.
- 15

Step 2: (4-Methanesulfonyl-phenyl)-methanesulfonyl chloride

- 20 To a solution of the (4-methanesulfonyl-phenyl)-methanethiol from Step 1 (7.3g, 36mmol) in AcOH (75mL) was added water (25mL). Then, chlorine was bubbled in the resulting mixture for 2min. The mixture was diluted with water and filtered to provide the (4-methanesulfonyl-phenyl)-methanesulfonyl chloride.

Step 3: C-(4-Methanesulfonyl-phenyl)-N,N-dimethyl-methanesulfonamide

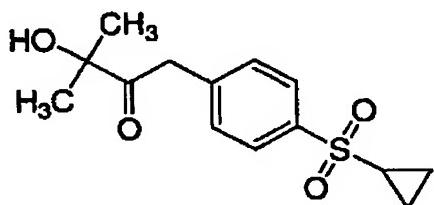
- 25 To a solution of (4-methanesulfonyl-phenyl)-methanesulfonyl chloride from Step 2 (1.0g, 3.7mmol) in CH₂Cl₂ (40mL) was added dimethylamine (0.42g, 9.3mmol) dropwise. After 18h, the resulting reaction mixture was diluted with a

saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (HCl 10%, NaHCO₃, brine), dried (MgSO₄), filtered, and concentrated to provided the C-(4-methanesulfonyl-phenyl)-N,N-dimethyl-methanesulfonamide compound.

5

Sulfone 09

1-(4-Cyclopropanesulfonyl-phenyl)-3-hydroxy-3-methyl-butan-2-one



10 **Step 1: 4-bromobenzene disulfide**

To a solution of 4-bromothiophenol (16g, 85mmol) in CH₂Cl₂ (85mL) was added iodine (10.7g, 42mmol, in CH₂Cl₂) and triethylamine (11.8mL, 85mmol). After 3h the resulting reaction mixture was diluted with a sodium bisulfite solution and ethyl acetate. The organic extracts were washed (1N NaOH, brine), dried (MgSO₄), filtered and concentrated. The resulting residue was stirred vigorously in hexane/ether for 1h then filtered to afford the 4-bromobenzene disulfide compound as a white powder.

15 **Step 2: 1-Bromo-4-cyclopropylsulfanyl-benzene**

20 Following the procedures described in **Sulfone 03, Step 2** and purification by flash chromatography (eluting with hexane) provided the 1-bromo-4-cyclopropylsulfanyl-benzene compound.

25 **Step 3: 1-(4-Cyclopropylsulfanyl-phenyl)-3-hydroxy-3-methyl-butan-2-one**

Following the procedures described in **Ketone 01**, but substituting the 1-bromo-4-cyclopropylsulfanyl-benzene from **Step 2** for 4-bromothioanisole, the 1-

(4-cyclopropylsulfanyl-phenyl)-3-hydroxy-3-methyl-butan-2-one compound was obtained.

Step 4: 1-(4-Cyclopropanesulfonyl-phenyl)-3-hydroxy-3-methyl-butan-2-one

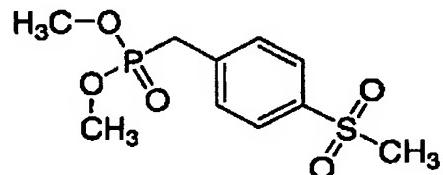
5 Following the procedures described in **Ketone 02**, but substituting the 1-(4-cyclopropylsulfanyl-phenyl)-3-hydroxy-3-methyl-butan-2-one from **Step 3** for **Ketone 01**, the 1-(4-cyclopropanesulfonyl-phenyl)-3-hydroxy-3-methyl-butan-2-one compound was obtained.

10

PREPARATION OF PHOSPHONATES

Phosphonate 01

15 (4-Methanesulfonyl-benzyl)-phosphonic acid dimethyl ester



Step 1: (4-Methylsulfanyl-benzyl)-phosphonic acid dimethyl ester

To trimethylphosphite (8.6g, 70mmol) at 140°C was added 4-methylthiobenzyl chloride (10g, 58mmol). The resulting mixture was stirred at 140°C for 18h, cooled at 21°C then diluted with HCl 10% and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered, and concentrated. Purification by flash chromatography (eluting with ethyl acetate) provided the (4-methylsulfanyl-benzyl)-phosphonic acid dimethyl ester compound.

25 **Step 2: (4-Methanesulfonyl-benzyl)-phosphonic acid dimethyl ester**

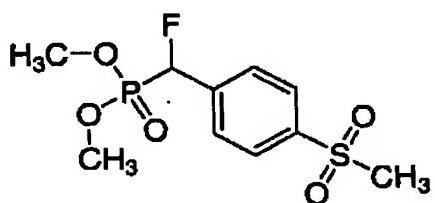
Following the procedures described in **Example 16**, but substituting (4-methylsulfanyl-benzyl)-phosphonic acid dimethyl ester from **Step 1** for **Example**

15, the (4-methanesulfonyl-benzyl)-phosphonic acid dimethyl ester compound was isolated.

5

Phosphonate 02

[Fluoro-(4-methanesulfonyl-phenyl)-methyl]-phosphonic acid dimethyl ester



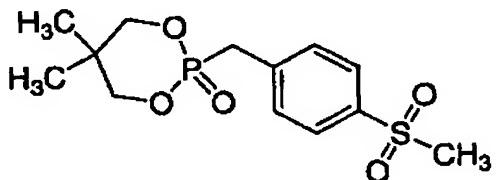
Following the procedures described in Example 37, but substituting
Phosphonate 01 for **Example 1**, using THF as solvent, and purification by flash
10 chromatography (eluting with toluene/acetone, 1:1) afforded the title compound.

10

Phosphonate 03

2-(4-Methanesulfonyl-benzyl)-5,5-dimethyl-[1,3,2]dioxaphosphinane 2-oxide

15



20

Step 1: (4-Methanesulfonyl-benzyl)-phosphonic acid

To a solution of **Phosphonate 01** (5.74g, 20.6mmol) in CHCl_3 (50mL)

was added TMSBr (27mL, 206mmol) dropwise. The resulting reaction mixture was stirred 18h at 21°C, concentrated under vacuum, and diluted with CHCl_3 and EtOH.

After 2h of stirring at 21°C, the mixture was concentrated again under vacuum. The resulting residue was crystallized from $\text{CH}_2\text{Cl}_2/\text{hexane}$ as a white solid.

Step 2: (4-Methanesulfonyl-benzyl)-phosphonoyl chloride

To a solution of (4-methanesulfonyl-benzyl)-phosphonic acid from Step 1 (5.3g, 21mmol) in CH₂Cl₂ (200mL) was added oxalyl chloride (4mL, 45mmol) dropwise and a few drops of DMF. After 5 days at 21°C, the solvent was evaporated and the residue was used as such in the next step.

5

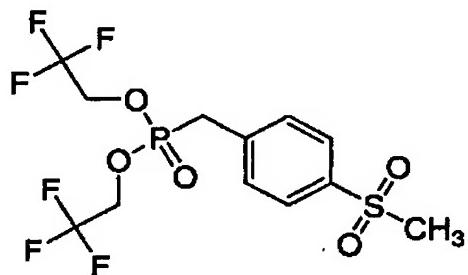
Step 3: 2-(4-Methanesulfonyl-benzyl)-5,5-dimethyl-[1,3,2]dioxaphosphinane 2-oxide

To a solution of (4-Methanesulfonyl-benzyl)-phosphonoyl chloride from Step 2 (100mg, 0.35mmol) in CH₂Cl₂ (5mL) was added triethylamine (0.1mL, 0.7mmol) and 2,2-dimethyl-1,3-propanediol (48mg, 0.47mmol). The resulting reaction mixture was stirred 48h at 21°C, then diluted with water and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by crystallization from CH₂Cl₂/hexane provided the 2-(4-methanesulfonyl-benzyl)-5,5-dimethyl-[1,3,2]dioxaphosphinane 2-oxide compound as a white solid.

15

Phosphonate 04

(4-Methanesulfonyl-benzyl)-phosphonic acid bis-(2,2,2-trifluoro-ethyl) ester



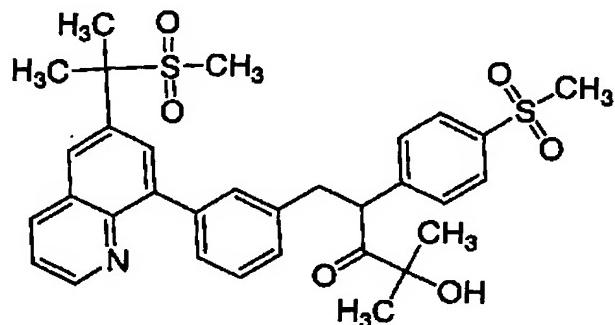
20

Following the procedures described in Phosphonate 03, but substituting 2,2,2-trifluoroethanol for 2,2-dimethyl-1,3-propanediol, the title compound was obtained.

25

EXAMPLE 1

4-Hydroxy-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-4-methyl-pentan-3-one



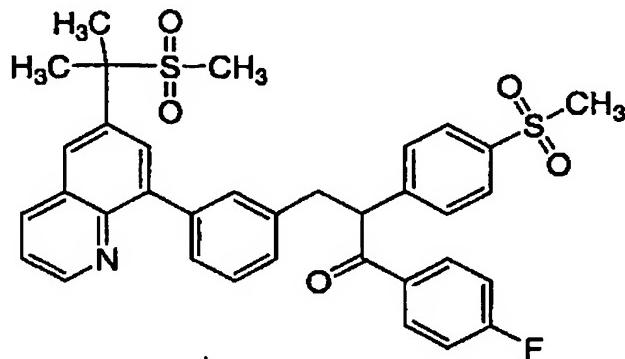
5 To a solution of Ketone 02 in THF/DMF (4:1, 0.08M) at 0°C was added potassium tert-butoxide (1M, THF, 1.0 eq) dropwise followed after 10 min by Quinoline 01 (1.0 eq) dissolved in DMF (2M). The resulting reaction mixture was stirred at 21°C for 3h and diluted with a saturated ammonium acetate solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄),
10 filtered, and concentrated. Purification by flash chromatography (eluting with ethyl acetate/dichloromethane, 60:40) provided the title compound as a white foam. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH, 65:35, retention time 12.26 and 13.36 min) to give Example 1A (first to elute, [α]_D 77.3 c = 0.94 CH₂Cl₂) and Example 1B.

15 ¹H NMR (400MHz, acetone-*d*6): δ 8.93 (dd, 1H), 8.45 (dd, 1H), 8.26 (d, 1H), 8.05 (d, 1H), 7.86 (d, 2H), 7.68 (d, 2H), 7.57 (m, 2H), 7.50 (d, 1H), 7.35 (t, 1H), 7.21 (d, 1H), 5.18 (dd, 1H), 4.46 (s, OH), 3.45 (dd, 1H), 3.08 (dd, 1H), 3.05 (s, 3H), 2.7 (s, 3H), 1.98 (s, 6H), 1.1 (s, 3H), 1.05 (s, 3H).

20

EXAMPLE 2

1-(4-Fluoro-phenyl)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one

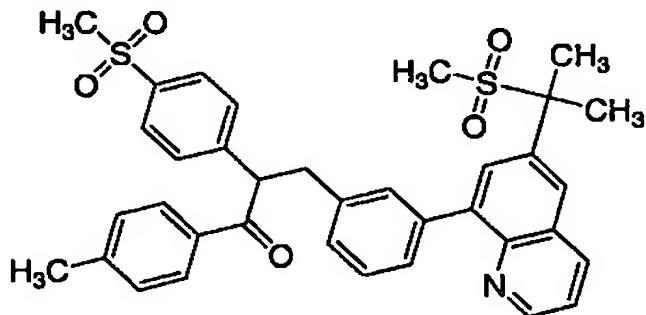


5 Following the procedures described in **Example 1**, but substituting
Ketone 03 for **Ketone 02**, the title compound was obtained as a white solid.

¹H NMR (400MHz, acetone-d₆): δ 8.88 (dd, 1H), 8.68 (dd, 1H), 8.43
(dd, 1H), 8.25 (d, 1H), 8.19-8.15 (m, 2H), 8.03 (d, 1H), 7.86 (d, 2H), 7.71 (d, 2H),
7.64 (s, 1H), 7.55 (dd, 1H), 7.50 (app d, 1H), 7.30 (t, 1H), 7.24 (app d, 1H), 7.19 (t,
10 2H), 5.47 (t, 1H), 3.22 (dd, 1H), 3.01 (s, 3H), 2.71 (s, 3H), 1.97 (s, 6H).

EXAMPLE 3

15 **3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-p-tolyl-propan-1-one**

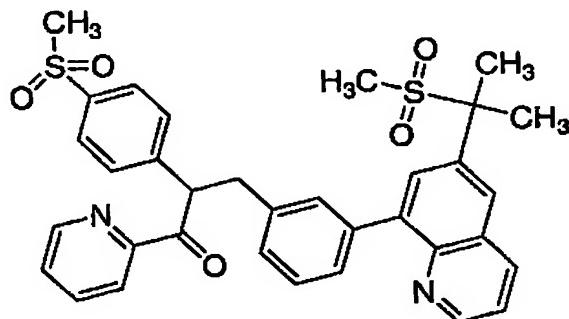


Following the procedures described in Example 1, but substituting Ketone 04 for Ketone 02, the title compound was obtained.

¹H NMR (400MHz, acetone-d₆): δ 8.88 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.02 (d, 1H), 7.98 (d, 2H), 7.85 (d, 2H), 7.71 (d, 2H), 7.64 (s, 1H), 7.55 (dd, 1H), 7.50 (app d, 1H), 7.30 (t, 1H), 7.25 (app d, 3H), 5.45 (t, 1H), 3.68 (dd, 1H), 3.20 (dd, 1H), 3.01 (s, 3H), 2.70 (s, 3H), 2.32 (s, 3H), 1.97 (s, 6H).

EXAMPLE 4

10 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-pyridin-2-yl-propan-1-one



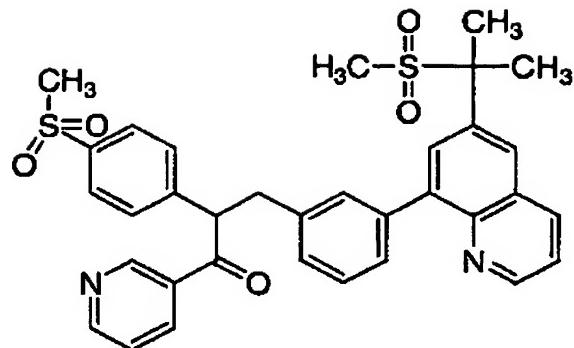
Following the procedures described in Example 1, but substituting
15 Ketone 05 for Ketone 02, the title compound was obtained.

¹H NMR (400MHz, acetone-d₆): δ 8.86 (dd, 1H), 8.69 (d, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.02-8.01 (m, 2H), 7.94 (td, 1H), 7.83 (d, 2H), 7.72 (d, 2H), 7.64 (s, 1H), 7.59-7.56 (m, 1H), 7.54 (dd, 1H), 7.50 (app d, 1H), 7.33-7.26 (m, 2H), 6.06 (t, 1H), 3.70 (dd, 1H), 3.27 (dd, 1H), 3.01 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

20

EXAMPLE 5

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-pyridin-3-yl-propan-1-one



Following the procedures described in **Example 1**, but substituting **Ketone 06** for **Ketone 02**, the title compound was obtained.

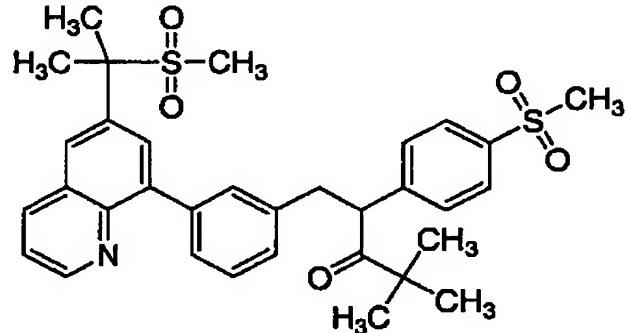
5 ¹H NMR (400MHz, acetone-*d*₆): δ 9.22 (d, 1H), 8.89 (dd, 1H), 8.69 (dd, 1H), 8.43 (dd, 1H), 8.36 (dt, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.87 (d, 2H), 7.73 (d, 2H), 7.65 (s, 1H), 7.55 (dd, 1H), 7.49 (app d, 1H), 7.45 (dd, 1H), 7.31 (t, 1H), 7.25 (app d, 1H), 5.52 (t, 1H), 3.70 (dd, 1H), 3.25 (dd, 1H), 3.01 (s, 3H), 2.71 (s, 3H), 1.97 (s, 6H).

10

EXAMPLE 6

1-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-4,4-dimethyl-pentan-3-one

15

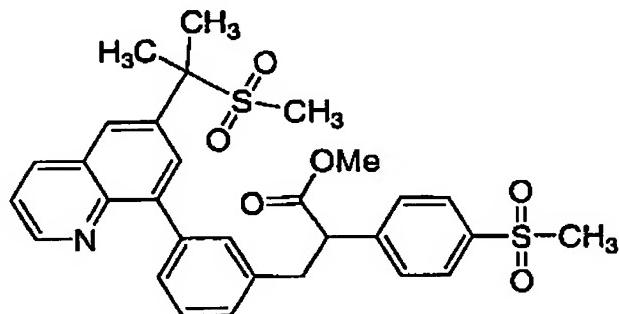


Following the procedures described in Example 1, but substituting Ketone 07 for Ketone 02, the title compound was obtained as white foam.

¹H NMR (400MHz, acetone-d₆): δ 8.93 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.04 (d, 1H), 7.87 (dd, 2H), 7.56 (m, 2H), 7.50 (d, 1H), 7.33 (t, 1H), 7.21 (d, 1H), 7.2 (dd, 2H), 4.89 (dd, 1H), 3.39 (dd, 1H), 3.06 (s, 3H), 3.04 (dd, 1H), 2.71 (s, 3H), 1.98 (s, 6H), 0.95 (s, 9H). 99254-47

EXAMPLE 7

10 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester

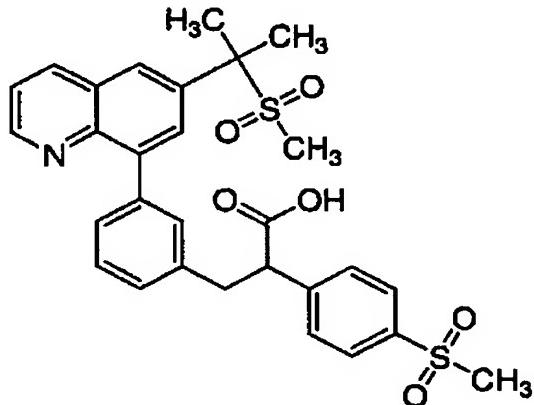


To a solution of Ester 01 (1.26g, 5.5mmol) in THF (80mL) at -78°C was added LiHMDS (1M, THF, 6.6mL, 6.6mmol) dropwise followed, after 30min, 15 Quinoline 01 (2.1g, 5.0mmol) dissolved in DMF (8mL). The reaction mixture was stirred at -78°C for 2h and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 40:60) provided the title compound as a white foam.

20 ¹H NMR (400MHz, acetone-d₆): δ 8.92 (dd, 1H), 8.43 (dd, 1H), 8.25 (d, 1H), 8.06 (d, 1H), 7.99 (d, 2H), 7.9 (d, 2H), 7.57 (m, 3H), 7.34 (t, 1H), 7.24 (d, 1H), 4.24 (t, 1H), 3.62 (s, 3H), 3.54 (dd, 1H), 3.29 (dd, 1H), 3.07 (s, 3H), 1.99 (s, 6H).

EXAMPLE 8

3-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid



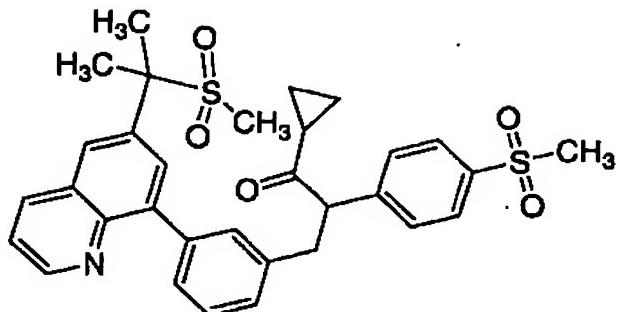
To a solution of Example 7 (130mg, 0.23mmol) in THF/MeOH/H₂O (2:2:1, 5mL) was added LiOH (2M, 0.35mL, 0.69mmol). The resulting mixture was stirred at 21°C 18h, acidified with HCl 10% and diluted with ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated.

10 The title compound was obtained as a white powder after sonication in ether/hexane and filtration.

¹H NMR (400MHz, acetone-d₆): δ 8.92 (dd, 1H), 8.43 (dd, 1H), 8.25 (d, 1H), 8.06 (d, 1H), 7.9 (d, 2H), 7.70 (d, 2H), 7.62 (s, 1H), 7.54 (m, 2H), 7.34 (t, 1H), 7.26 (d, 1H), 4.22 (dd, 1H), 3.55 (dd, 1H), 3.39 (dd, 1H), 3.07 (s, 3H), 2.71 (s, 15 3H), 1.98 (s, 6H).

EXAMPLE 9

1-Cyclopropyl-3-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-2-(4-methanesulfonyl-phenyl)-propan-1-one



Step 1: 3-[3-{6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-N-methoxy-N-methyl-propionamide

5 To a solution of N,O-dimethylhydroxylamine (free base, 260mg, 4.2mmol) in THF at -78°C was added MeMgBr (3M, ether, 1.4mL, 4.2mmol) dropwise (internal temperature < -65°C) followed, after 30 min, by Example 7 (600mg, 1.06mmol, in THF). The resulting mixture was warmed slowly to 21°C, diluted with ethyl acetate and saturated ammonium chloride solution. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered, and concentrated.

10 Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:4 to 1:9) provided the 3-[3-{6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-N-methoxy-N-methyl-propionamide compound as a white foam.

15 **Step 2:** 1-Cyclopropyl-3-[3-{6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one

Anhydrous CeCl₃ (266mg, 1.26mmol) was heated 2h at 130°C under high vacuum, refluxed in THF (10mL) for 1h then cooled to 0°C. To the resulting white suspension at 0°C was added freshly prepared cyclopropylmagnesium bromide (0.6M, THF, 2.1mL, 1.25mmol) and the resulting mixture stirred at 0°C for 1h then cooled to -78°C. The 3-[3-{6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-N-methoxy-N-methyl-propionamide from Step 1 (in THF, 150 mg, 0.25mmol) was added and the mixture warmed to 0°C for

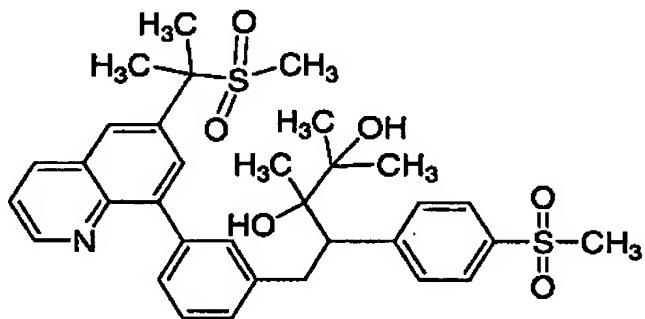
1h, diluted with ethyl acetate and saturated ammonium chloride solution. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:4) provided the 1-cyclopropyl-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one compound as a white foam.

5 1H NMR (400MHz, acetone-*d*6): δ 8.93 (dd, 6H), 8.42 (dd, 1H), 8.25 (d, 1H), 8.06 (d, 1H), 7.95 (d, 2H), 7.63 (d, 2H), 7.54 (m, 3H), 7.31 (t, 1H), 7.20 (d, 1H), 4.61 (t, 1H), 3.56 (dd, 1H), 3.09 (dd, 1H), 3.05 (s, 3H), 2.71 (s, 3H), 2.06 (m, 1H), 1.98 (s, 6H), 0.9-0.7 (m, 4H).

10 An alternate synthesis of Example 9 is by following the procedures described above in Example 1, but substituting Ketone 08 for Ketone 02.

EXAMPLE 10

15 5-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-(4-methanesulfonyl-phenyl)-2,3-dimethyl-pentane-2,3-diol



20 Using Example 01 as the starting material and following the procedures described above in Example 9, Step 2, and substituting methylmagnesium bromide for cyclopropyl magnesium bromide, the title compound was obtained as a white solid (one pair of enantiomer).

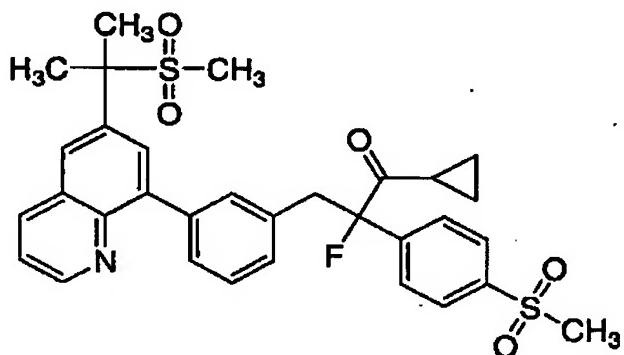
1H NMR (400MHz, acetone-*d*6): δ 8.89 (dd, 1H), 8.38 (dd, 1H), 8.20 (d, 1H), 7.95 (d, 1H), 7.71 (d, 2H), 7.61 (d, 2H), 7.50 (dd, 1H), 7.47 (s, 1H), 7.39 (d,

1H), 7.16 (t, 1H), 7.08 (d, 1H), 3.74 (m, 2H), 3.63 (s, 1H), 3.29 (s, 1H), 3.19 (m, 1H), 2.93 (s, 3H), 2.70 (s, 3H), 1.95 (s, 6H), 1.41 (s, 6H), 1.32 (s, 3H).

5

EXAMPLE 11

1-Cyclopropyl-2-fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-one



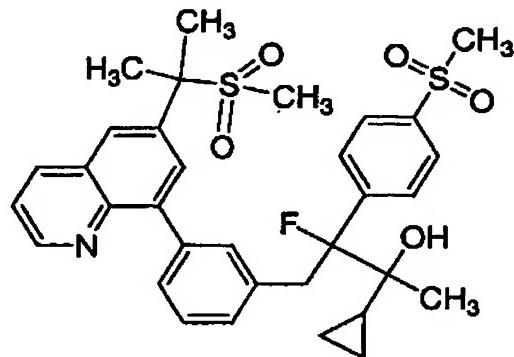
10

To a solution of Example 9 (1.5g, 2.62mmol) in THF/DMF (3:1, 13mL) at -78°C was added potassium tert-butoxide (1M THF, 2.9mL, 2.9mmol), followed by N-fluorobenzenesulfonimide (1.63g, 5.2mmol). The resulting reaction mixture was stirred 2h at -78°C, then quenched with AcOH (2 drops) and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 80:20) provided the title compound.

15 ¹H NMR (400MHz, acetone-d6): δ 8.90 (dd, 1H), 8.40 (dd, 1H), 8.24 (d, 1H), 8.05 (d, 1H), 7.97 (d, 2H), 7.71 (d, 2H), 7.59 (d, 1H), 7.55 (s, 1H), 7.53 (dd, 1H), 7.34 (t, 1H), 7.14 (d, 1H), 3.78 (dd, 1H), 3.52 (dd, 1H), 3.09 (s, 3H), 2.70 (s, 3H), 2.49-2.41 (m, 1H), 1.98 (s, 6H), 0.91-0.85 (m, 4H).

EXAMPLE 12

2-Cyclopropyl-3-fluoro-4-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-3-(4-methanesulfonyl-phenyl)-butan-2-ol



Using Example 11 as starting material and following the procedures described below in Example 29, the title compound was obtained as a white solid (9:1 mixture of diastereoisomers). The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH, 1:1, retention time 21 and 29 min) to give Example 12A and Example 12B.

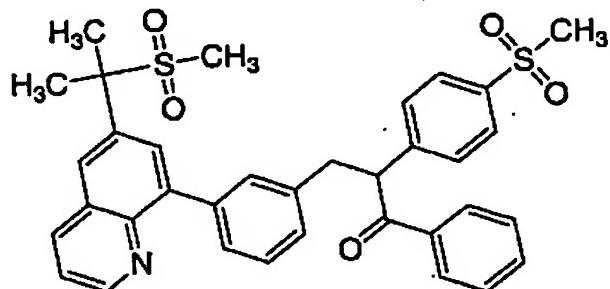
¹H NMR (400MHz, acetone-d6): (major isomer) δ 8.88 (dd, 1H), 8.38 (dd, 1H), 8.20 (d, 1H), 7.91 (d, 1H), 7.83 (d, 2H), 7.78 (d, 2H), 7.51 (dd, 1H), 7.45 (s, 1H), 7.44 (d, 1H), 7.18 (t, 1H), 7.14 (d, 1H), 4.11 (s, OH), 3.83 (s, 1H), 3.77 (dd, 1H), 2.97 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.34 (d, 3H), 0.96-0.92 (m, 1H), 0.34-0.22 (m, 3H), 0.14-0.10 (m, 1H). LRMS (CI) 610 (M+H)⁺.

The other pair of enantiomers can be obtained using Example 14 as the starting material and following procedures described in Example 11 followed with the procedures described above in Example 9, Step 2 (85:15 mixture of diastereoisomers).

¹H NMR (400MHz, acetone-d6): δ 8.88 (dd, 1H), 8.40 (dd, 1H), 8.21 (d, 1H), 7.91 (d, 1H), 7.79 (m, 4H), 7.52 (dd, 1H), 7.43 (m, 2H), 7.15 (m, 2H), 4.1-3.6 (m, 3H), 3.89 (s, 3H), 2.70 (s, 3H), 1.97 (d, 6H), 1.29 (m, 1H), 1.09 (d, 3H), 0.81 (m, 1H), 0.56 (m, 1H), 0.38 (m, 2H).

EXAMPLE 13

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-phenyl-propan-1-one



5

Step 1: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methysulfanyl-phenyl)-propionic acid methyl ester

To a solution of Ester 04 (4.0g, 20mmol) in THF (50mL) at -78°C was added KHMDS (0.5M, Tol, 41mL, 20.5mmol) dropwise. The resulting reaction mixture was stirred 0.5h at -78°C then cannulated into Quinoline 02 (2.95g, 6.8mmol) in THF (50mL) at 21°C. After 15min, the mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methysulfanyl-phenyl)-propionic acid methyl ester compound as a white foam.

Step 2: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methysulfanyl-phenyl)-propionaldehyde

To a solution of 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methysulfanyl-phenyl)-propionic acid methyl ester from Step 1 (1.48g, 7.5mmol) in CH₂Cl₂ (80mL) at -78°C was added dibal-H (1.6mL, 7.8mmol). The resulting reaction mixture was stirred 1h at -78°C, then quenched with sodium potassium tartrate solution and stirred at 21°C for 3h. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated to provided the 3-{3-

[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionaldehyde compound as a white foam.

Step 3: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-

- 5 **methylsulfanyl-phenyl)-1-phenyl-propan-1-ol**

To a solution of 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionaldehyde from Step 2 (150mg, 0.3mmol) in CH₂Cl₂ (6mL) at 21°C was added phenylmagnesium chloride (2M, THF, 0.45mL, 0.9mmol) dropwise. The resulting reaction mixture was stirred 0.5h at 21°C

- 10 then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. The crude oil was used as such in the next step.

Step 4: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-

- 15 **methylsulfanyl-phenyl)-1-phenyl-propan-1-one**

To a solution of the crude oil from Step 3 in CH₂Cl₂ (5mL) at 21°C was added Dess-Martin periodinane (255mg, 0.6mmol) portionwise. The resulting reaction mixture was stirred 2h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-1-phenyl-propan-1-one compound as a white foam.

- 25 **Step 5: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-**
- methanesulfonyl-phenyl)-1-phenyl-propan-1-one

To a solution of 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-1-phenyl-propan-1-one from Step 4 (55mg, 0.095mmol) in THF/MeOH/H₂O (2:1:1, 5mL) at 21°C was added OXONE® (0.1g, 0.16mmol). The resulting reaction mixture was stirred 2h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were

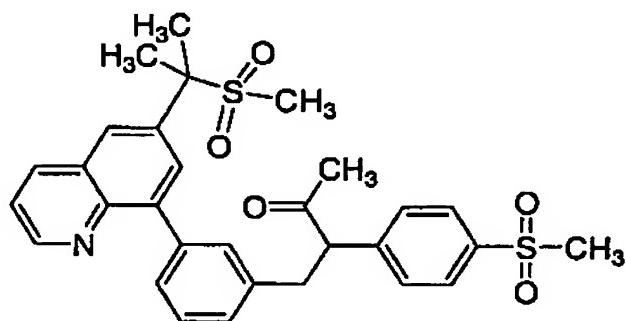
washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated. The residue was stirred vigorously in hexane/ether for 1 h then filtered to afford the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-1-phenyl-propan-1-one compound as a white powder.

5 1H NMR (400MHz, acetone-*d*6): δ 8.87 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.08 (d, 2H), 8.03 (d, 1H), 7.85 (d, 2H), 7.71 (d, 2H), 7.65 (s, 1H), 7.56-7.42 (m, 5H), 7.28 (m, 2H), 5.5 (t, 1H), 3.69 (dd, 1H), 3.23 (dd, 1H), 3.00 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H). **99020-173**

10

EXAMPLE 14

4-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-one



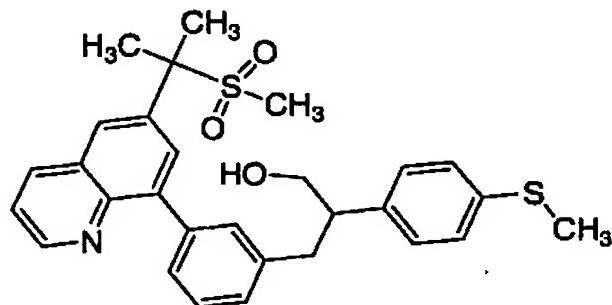
15

Following the procedures described above in Example 13, but substituting methylmagnesiumbromide for phenylmagnesium bromide in Step 3, the title compound was obtained as a white solid.

15 1H NMR (400MHz, acetone-*d*6): δ 8.92 (dd, 1H), 8.43 (dd, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.95 (d, 2H), 7.62 (d, 2H), 7.60-7.52 (m, 3H), 7.31 (t, 1H), 7.18 (d, 1H), 4.50 (t, 1H), 3.52 (dd, 1H), 3.10 (dd, 1H), 3.05 (s, 3H), 2.83 (s, 3H), 2.11 (s, 3H), 1.98 (s, 6H).

EXAMPLE 15

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propan-1-ol



To a solution of the ester from **Step 1, Example 13** (1.0g, 5mmol) in

5 CH₂Cl₂ (25mL) at -78°C was added dibal-H (2.1mL, 12mmol). The resulting reaction mixture was warmed slowly to 21°C, then quenched with sodium potassium tartrate solution and stirred at 21°C for 3h. The reaction mixture was diluted with ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl

10 acetate, 50:50) provided the title compound as a white foam.

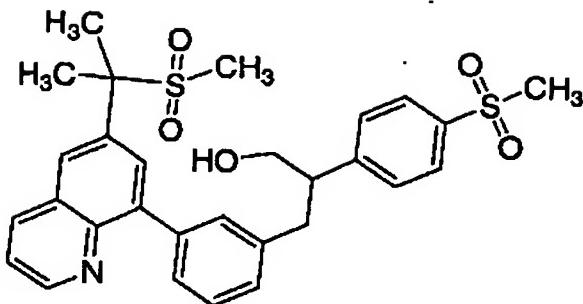
¹H NMR (400MHz, acetone-*d*6): δ 8.91 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.01 (d, 1H), 7.56 (dd, 1H), 7.51 (m, 2H), 7.29 (t, 1H), 7.24-7.14 (m, 6H), 3.75 (d, 2H), 3.27 (dd, 1H), 3.14 (m, 1H), 2.96 (dd, 1H), 2.70 (s, 3H), 2.42 (s, 3H), 1.98 (s, 6H).

15

EXAMPLE 16

3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol

20



To a solution of Example 15 (350mg, 0.69mmol) in THF/MeOH/H₂O (2:1:1, 15mL) at 21°C was added OXONE® (1.1g, 1.8mmol). The resulting reaction mixture was stirred 2h at 21°C then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated to afford the title compound as a pale yellow foam.

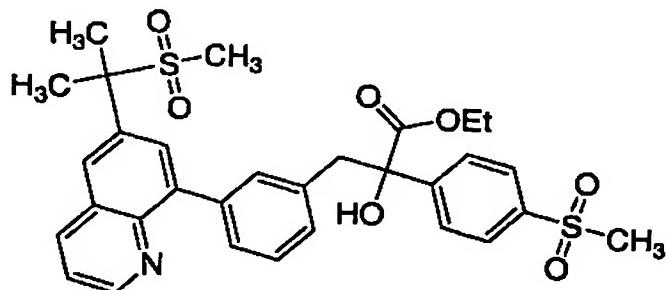
¹H NMR (400MHz, acetone-d6): δ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.04 (d, 1H), 7.82 (d, 2H), 7.55 (m, 5H), 7.31 (t, 1H), 7.20 (d, 1H), 3.83 (d, 2H), 3.34 (m, 2H), 3.05 (m, 1H), 3.03 (s, 3H), 2.70 (s, 3H), 1.98 (s, 6H).

10

EXAMPLE 17

2-Hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester

15



Step 1: 2-Hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester

To a solution of Ester 02 (220mg, 0.97mmol) in THF (6mL) at -78°C was added potassium tert-butoxide (1M, THF, 2.1mL, 2.1mmol) dropwise. The resulting reaction mixture was warmed to -40°C for 20 min, then Quinoline 01 (0.25M, THF, 3mL) was added. The reaction mixture was warmed from -40°C to 5 -20°C over a 2h period, then quenched with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the 2-hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionic acid ethyl ester compound as a white foam.

10

Step 2: 2-Hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester

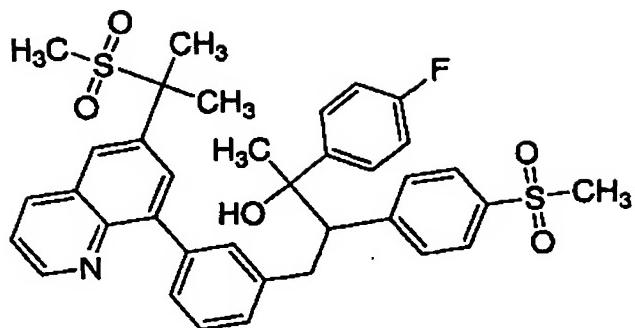
15 Using the 2-hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester from Step 1 and following the procedures described in Example 16, and purification by flash chromatography (eluting with hexane/ethyl acetate, 1:4) provided the 2-hydroxy-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester compound as a white foam.

20 ¹H NMR (400MHz, acetone-*d*6): δ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.25 (d, 1H), 8.07 (d, 1H), 8.02 (d, 2H), 7.93 (d, 2H), 7.65 (s, 1H), 7.56 (m, 2H), 7.33 (m, 2H), 5.07 (s, OH), 4.17 (m, 2H), 3.71 (d, 1H), 3.33 (d, 1H), 3.07 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H), 1.17 (m, 3H).

25

EXAMPLE 18

2-(4-Fluoro-phenyl)-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol



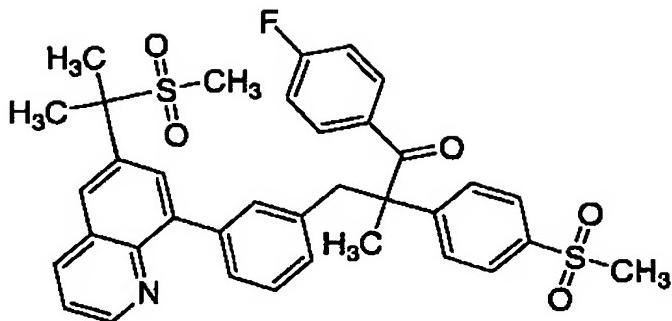
To a solution of Example 02 (101mg, 0.16mmol) in THF (2mL) at 21°C was added methyl magnesium iodide (3M, Et₂O, 0.3mL, 0.9mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 18h, then diluted with a 5 saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 85:15) provided the title compound as a mixture of diastereoisomers (5:1).

¹H NMR (400MHz, acetone-d₆): δ 8.87 (dd, 1H), 8.38 (dd, 1H), 8.20 (d, 1H), 7.93 (d, 1H), 7.76-7.73 (m, 1H), 7.60 (d, 2H), 7.51 (dd, 1H), 7.41-7.33 (m, 5H), 7.17 (d, 1H), 7.12 (t, 1H), 7.07 (d, 1H), 6.93 (t, 1H), 4.50 (s, OH), 3.62 (dd, 1H), 3.54 (dd, 1H), 3.17 (t, 1H), 2.89 (s, 3H), 2.69 (s, 3H), 1.95 (s, 6H), 1.78 (s, 3H). LRMS (CI) 646 (M+H)⁺.

15

EXAMPLE 19

1-(4-Fluoro-phenyl)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-2-methyl-propan-1-one



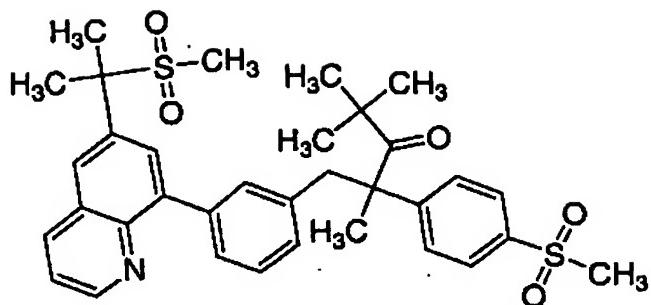
To a solution of **Ketone 09** (171g, 0.56mmol) in THF (3mL) at -20 °C was added potassium tert-butoxide (1M, 0.59mL, 0.59mmol) dropwise followed, after 15min, by **Quinoline 01** (250mg, 0.59mmol) dissolved in DMF (0.4mL). The 5 resulting reaction mixture was stirred at 21°C for 3h and diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 85:15) followed by stirring vigorously in hexane/ethyl acetate/ether for 1h then filtered to afford the title compound as a 10 white powder.

¹H NMR (400MHz, acetone-d6): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.02 (d, 1H), 7.85 (d, 2H), 7.64-7.61 (m, 2H), 7.55 (dd, 1H), 7.50 (d, 3H), 7.21 (d, 1H), 7.18 (s, 1H), 7.08-7.04 (m, 2H), 6.69 (d, 1H), 3.54 (d, 1H), 3.46 (d, 1H), 2.84 (s, 3H), 2.71 (s, 3H), 1.97 (s, 6H), 1.77 (s, 3H). LRMS (CI) 644 (M+H)⁺.

15

EXAMPLE 20

1-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-2-(4-methanesulfonyl-phenyl)-2,4,4-trimethyl-pentan-3-one

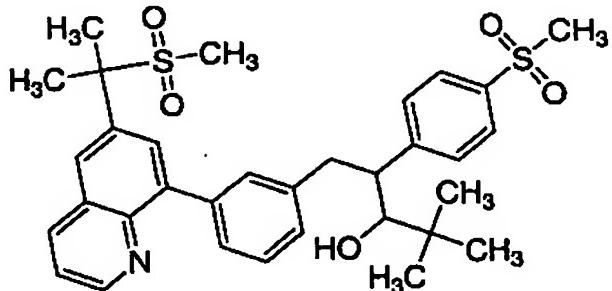


Following the procedures described in **Example 19**, but substituting **Ketone 10** for **Ketone 09** and purification by flash chromatography (eluting with dichloromethane/methanol, 99:1), then stirring vigorously the resulting solid in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder.

¹H NMR (400MHz, acetone-d6): δ 8.91 (dd, 1H), 8.40 (dd, 1H), 8.22 (d, 1H), 8.01 (d, 1H), 7.83 (d, 2H), 7.53 (dd, 1H), 7.46 (dd, 1H), 7.36 (dd, 2H), 7.14 (t, 1H), 7.09 (s, 1H), 6.55 (s, 1H), 3.28 (d, 1H), 3.18 (d, 1H), 2.81 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.77 (s, 3H), 1.00 (s, 9H). LRMS (CI) 606 (M+H)⁺.

EXAMPLE 21

1-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-4,4-dimethyl-pentan-3-ol



To a solution of **Example 06** (75mg, 0.127mmol) in MeOH (3mL) at -78°C was added sodium borohydride (5mg, 0.13mmol). The resulting reaction mixture was warmed to 21°C then diluted with a saturated ammonium chloride

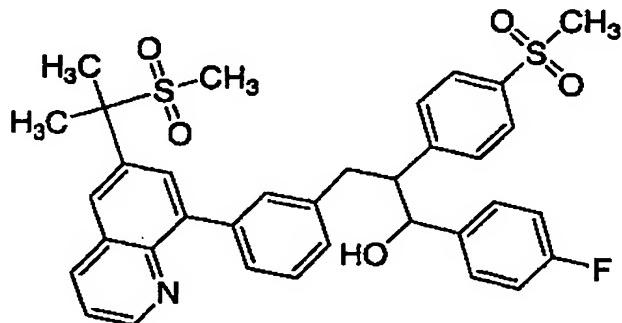
solution and ethyl acetate. The organic extracts were washed (H_2O), (brine), dried ($MgSO_4$), filtered and concentrated to provide the title compound as a white foam (one pair of enantiomer).

¹H NMR (400MHz, acetone-*d*6): δ 8.93 (dd, 1H), 8.45 (dd, 1H), 8.25 (d, 1H), 8.07 (d, 1H), 7.78 (m, 4H), 7.59 (m, 2H), 7.49 (d, 1H), 7.31 (t, 1H), 7.19 (d, 1H), 4.34 (d, OH), 3.66 (m, 1H), 3.45 (m, 1H), 3.29 (dd, 1H), 3.09 (dd, 1H), 3.0 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H), 0.71 (s, 9H). 99254-62

10

EXAMPLE 22

1-(4-Fluoro-phenyl)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol

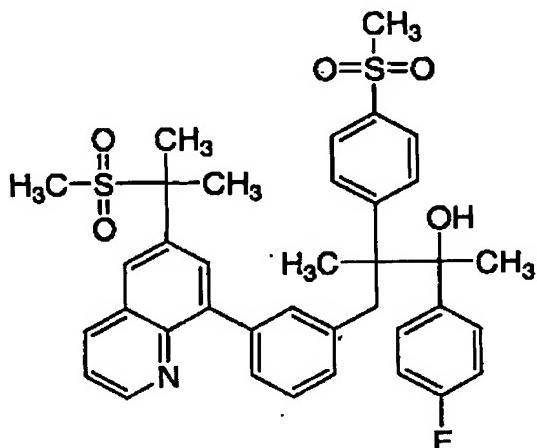


Following the procedures described in Example 21, but substituting
 15 Example 02 for Example 06 and purification by flash chromatography (eluting with dichloromethane/methanol, 99:1), then stirring vigorously the resulting residue in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder (one pair of enantiomer).

¹H NMR (400MHz, acetone-*d*6): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.03 (d, 1H), 7.72 (d, 2H), 7.56-7.53 (m, 2H); 7.49-7.44 (m, 3H), 7.31-7.23 (m, 3H), 7.18 (d, 1H), 7.00-6.95 (m, 2H), 5.11 (t, 1H), 4.65 (d, OH), 3.53-3.50 (m, 1H), 3.27 (dd, 1H), 3.15 (d, 1H), 2.99 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 23

2-(4-Fluoro-phenyl)-4-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-3-(4-methanesulfonyl-phenyl)-3-methyl-butan-2-ol



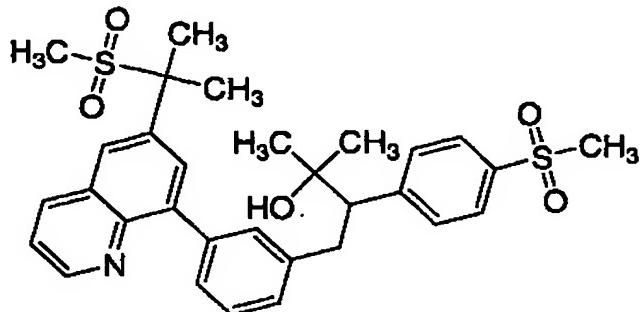
5 To a solution of Example 19 (93mg, 0.144mmol) in CH₂Cl₂ (4mL) at -78°C was added methyl magnesium iodide (3M, Et₂O, 0.24mL, 0.8mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 12h, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by
10 flash chromatography (eluting with dichloromethane/methanol, 99:1, 2 X), then stirring vigorously the resulting residue in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder (mixture of diastereoisomers; 1:1).

15 ¹H NMR (400MHz, acetone-d6): δ 8.87-8.80 (m, 2H), 8.41-8.35 (m, 2H), 8.19-8.15 (m, 2H), 7.94 (d, 1H), 7.91 (d, 1H), 7.85-7.78 (m, 4H), 7.70-7.66 (d, 2H), 7.61-7.35 (m, 11H), 7.21-7.08 (m, 4H), 7.05-6.98 (m, 3H), 6.86-6.81 (m, 3H), 4.44 (d, 1H), 4.03 (d, 1H), 3.93 (d, 1H), 3.27 (d, 1H), 2.96 (s, 3H), 2.94 (s, 3H), 2.68 (s, 3H), 2.67 (s, 3H), 1.96-1.94 (m, 12H), 1.80 (s, 3H), 1.50 (s, 6H), 1.39 (s, 3H). LRMS (CI) 660 (M+H)⁺.

20

EXAMPLE 24

4-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-3-(4-methanesulfonyl-phenyl)-2-methyl-butan-2-ol



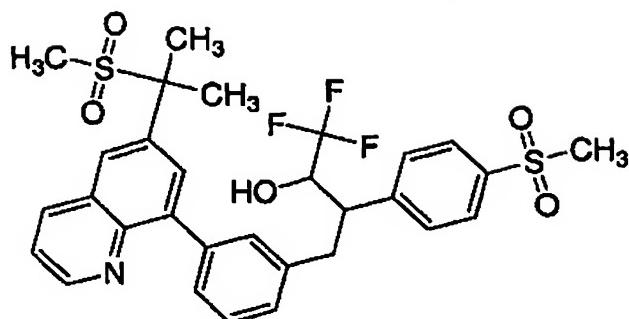
To a solution of Example 07 (230mg, 0.41mmol) in THF/CH₂Cl₂ (1:1, 5mL) at 21°C was added methyl magnesium bromide (3M, Et₂O, 1.0 mL, 3mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 0.25h, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with ethyl acetate/hexane, 70:30) afforded the title compound as a white foam.

¹H NMR (400MHz, acetone-*d*6): δ 8.88 (dd, 1H), 8.39 (dd, 1H), 8.21 (d, 1H), 7.94 (d, 1H), 7.77 (d, 2H), 7.61 (d, 2H), 7.52 (dd, 1H), 7.41 (m, 2H), 7.21 (t, 1H), 7.10 (d, 1H), 3.75 (s, OH), 3.52 (m, 3H), 3.26 (m, 1H), 2.98 (s, 3H), 2.70 (s, 3H), 1.96 (s, 6H), 1.5 (s, 3H), 1.17 (s, 3H).

15

EXAMPLE 25

1,1,1-Trifluoro-4-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-3-(4-methanesulfonyl-phenyl)-butan-2-ol



Step 1: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionaldehyde

Following the procedures described in Example 13, Step 2, but substituting Example 07 for the ester from Step 1, the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionaldehyde compound was isolated as a white foam.

Step 2: 1,1,1-Trifluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol

To a solution of 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionaldehyde from Step 1 (413mg, 0.8mmol) in THF (10mL) at -78°C was added TMSCF₃ (0.4mL, 2.7mmol) followed by tetrabutylammonium fluoride (1M, THF, 0.12mL, 120mmol). The resulting reaction mixture was warmed to 0°C, then quenched with tetrabutylammonium fluoride (1M, THF, 1mL, 1mmol). After 1h, the resulting solution was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 60:40 to 10:90) and sonication in hexane/ethyl acetate/ether provided the 1,1,1-trifluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-butan-2-ol compound as a white powder (mixture of diastereoisomers).

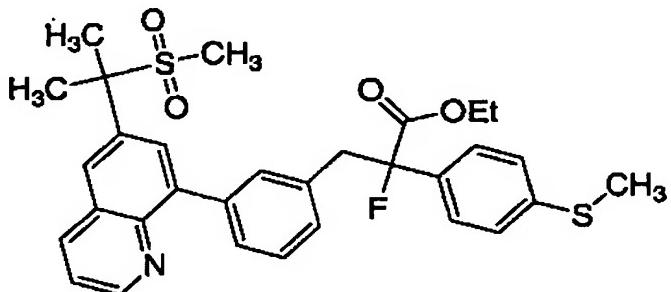
¹H NMR (400MHz, acetone-d6, major isomer): δ 8.91 (dd, 1H), 8.43 (dd, 1H), 8.22 (d, 1H), 7.98 (d, 1H), 7.8 (m, 2H), 7.57 (m, 3H), 7.43 (s, 1H), 7.23 (t,

1H), 7.04 (d, 1H), 5.88 (m, OH), 4.5 (m, 1H), 3.6 (m, 2H), 3.2 (m, 1H), 3.04 (s, 3H), 1.97 (s, 6H).

5

EXAMPLE 26

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfonyl-phenyl)-propionic acid ethyl ester



To a solution of Ester 03 (3.4g, 13mmol) and Quinoline 01 (4.5g,

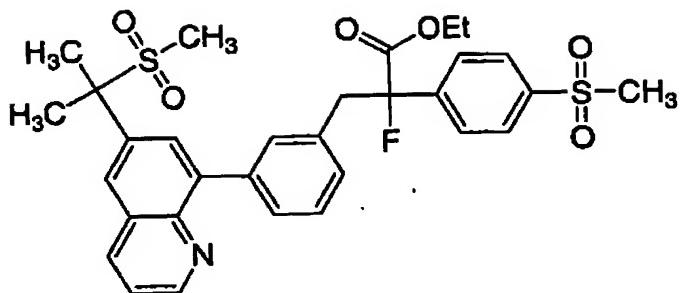
- 10 11mmol) in THF/DMF (2:1, 60mL) at 0°C was added potassium tert-butoxide (1M, THF, 13.9mL, 13.9mmol) dropwise. After 30min. at 0°C, the resulting reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 15 9:1) provided the title compound.

¹H NMR (400MHz, acetone-d₆): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.05 (d, 1H), 7.63-7.53 (m, 5H), 7.40-7.29 (m, 4H), 4.15 (q, 2H), 3.80 (dd, 1H), 3.53 (dd, 1H), 2.70 (s, 3H), 2.49 (s, 3H), 1.99 (s, 6H), 1.12 (t, 3H).

20

EXAMPLE 27

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid ethyl ester



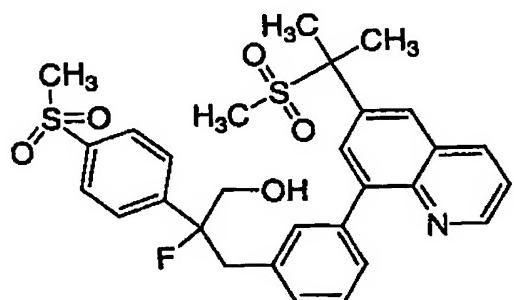
Following the procedures described in **Example 16**, but substituting **Example 26** for **Example 15**, the title compound was obtained.

¹H NMR (400MHz, acetone-*d*₆): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.06 (d, 1H), 8.01 (d, 2H), 7.90 (app d, 2H), 7.64-7.62 (m, 2H), 7.56 (dd, 1H), 7.38 (t, 1H), 7.30 (d, 1H), 4.20 (q, 2H), 3.88 (dd, 1H), 3.60 (dd, 1H), 3.10 (s, 3H), 2.71 (s, 3H), 1.99 (s, 6H), 1.19 (t, 3H).

10

EXAMPLE 28

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol



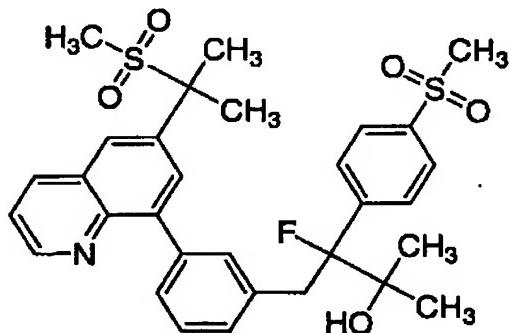
To a solution of Example 27 (1.15g, 1.95mmol) in CH₂Cl₂ (80mL) at -78°C was added dibal-H (0.82mL, 4.6mmol). The resulting reaction mixture was stirred 1h at -78°C, then quenched with sodium potassium tartrate solution and stirred at 21°C for 3h. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), 5 filtered and concentrated. To the residue dissolved in THF/MeOH (2:1, 22mL) at 21°C was added NaBH₄ (180mg, 4.9mmol). After 12h, the reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated to provided the title compound as a white solid.

10 ¹H NMR (400MHz, acetone-d₆): δ 8.90 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.02 (d, 1H), 7.89 (d, 2H), 7.68 (d, 2H), 7.60-7.50 (m, 3H), 7.29 (t, 1H), 7.15 (d, 1H), 4.42 (t, OH), 4.03 (dd, 1H), 3.98 (dd, 1H), 3.58 (dd, 1H), 3.44 (dd, 1H), 3.03 (s, 3H), 2.71 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H).

15

EXAMPLE 29

3-Fluoro-4-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-3-(4-methanesulfonyl-phenyl)-2-methyl-butan-2-ol



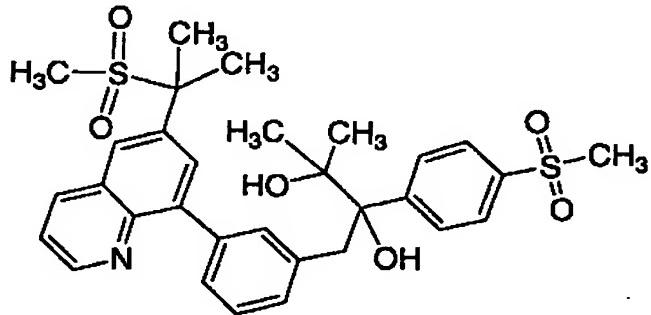
20 Anhydrous CeCl₃ (658mg, 2.67mmol) was heated 1h at 130°C under high vacuum. It was refluxed in THF (8mL) for 1h and then cooled to 0°C. To the resulting white suspension at 0°C, was added methylmagnesium bromide (3M, THF, 0.89mL, 2.7mmol). The resulting mixture was stirred at 0°C for 1h. Example 27 (267mg, 0.45mmol), dissolved in THF (1mL) was added, and the mixture stirred at

0°C for 0.5h, and diluted with ethyl acetate and saturated ammonium chloride solution. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 9:1) and stirring vigorously in ethyl acetate/ether for 1h, then filtering afforded the title compound as a white powder. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH, 50:50, retention time 6.82 and 9.27 min) to give **Example 29A** and **Example 29B**.

¹H NMR (400MHz, acetone-d₆): δ 8.88 (dd, 1H), 8.40 (dd, 1H), 8.21 (d, 1H), 7.91 (d, 1H), 7.82 (d, 2H), 7.75 (app d, 2H), 7.53 (dd, 1H), 7.44 (d, 1H), 7.41 (s, 1H), 7.17 (t, 1H), 7.11 (d, 1H), 4.29 (s, OH), 3.77-3.54 (m, 2H), 2.96 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.42 (s, 3H), 1.11 (s, 3H).

EXAMPLE 30

15 1-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-3-methyl-butane-2,3-diol



Following the procedures described in **Example 29**, but substituting **Example 17** for **Example 27** and purification by flash chromatography (eluting with toluene/acetone, 80:20 afforded the title compound as a white powder.

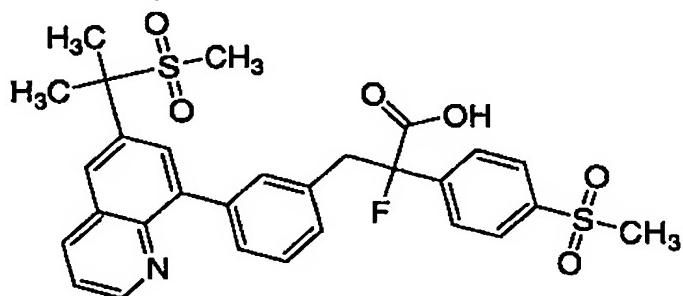
¹H NMR (400MHz, acetone-d₆): δ 8.88 (dd, 1H), 8.40 (dd, 1H), 8.21 (d, 1H), 7.95 (d, 1H), 7.93 (d, 2H), 7.80 (d, 2H), 7.53 (dd, 1H), 7.50 (s, 1H), 7.42 (dt, 1H), 7.18-7.12 (m, 2H), 4.08 (s, OH), 4.06 (s, OH), 3.75 (d, 1H), 3.49 (d, 1H), 2.97 (s,

3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H). LRMS (CI) 582 (M+H)⁺.

5

EXAMPLE 31

2-Fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propionic acid



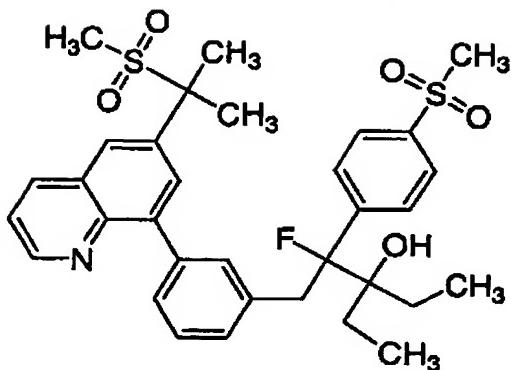
Following the procedures described in Example 08, but substituting

- 10 **Example 27 for Example 07** and using only 1.5 equivalent of LiOH, the title compound was obtained as a white solid.

¹H NMR (400MHz, acetone-d₆): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.06 (d, 1H), 8.01 (d, 2H), 7.92 (d, 2H), 7.66 (s, 1H), 7.63 (dd, 1H), 7.56 (dd, 1H), 7.37 (t, 1H), 7.32 (d, 1H), 3.90 (dd, 1H), 3.62 (dd, 1H), 3.10 (s, 3H), 2.72 (s, 3H), 1.99 (s, 3H), 1.99 (s, 3H).

EXAMPLE 32

- 20 **3-Ethyl-2-fluoro-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-pentan-3-ol**

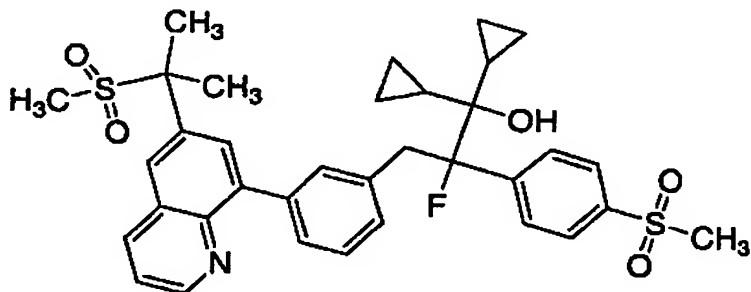


Following the procedures described above in Example 29, but substituting ethylmagnesium bromide for methylmagnesium bromide and purification by flash chromatography (eluting with toluene/acetone, 9:1) afforded the title compound as a white foam.

¹H NMR (400MHz, acetone-d₆): δ 8.90 (dd, 1H), 8.41 (dd, 1H), 8.21 (d, 1H), 7.92 (d, 1H), 7.81-7.75 (m, 4H), 7.54 (dd, 1H), 7.43 (d, 1H), 7.35 (s, 1H), 7.16 (t, 1H), 7.05 (d, 1H), 4.07 (s, OH), 3.75-3.59 (m, 2H), 2.93 (s, 3H), 2.71 (s, 3H), 2.01-1.90 (m, 2H), 1.98 (s, 3H), 1.97 (s, 3H), 1.45-1.32 (m, 2H), 1.02 (dt, 3H), 0.82 (dt, 3H). LRMS (CI) 612 (M+H)⁺.

EXAMPLE 33

1,1-Dicyclopropyl-2-fluoro-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-propan-1-ol



Following the procedures described above in Example 29, but substituting cyclopropyl magnesium bromide for methyl magnesium bromide and

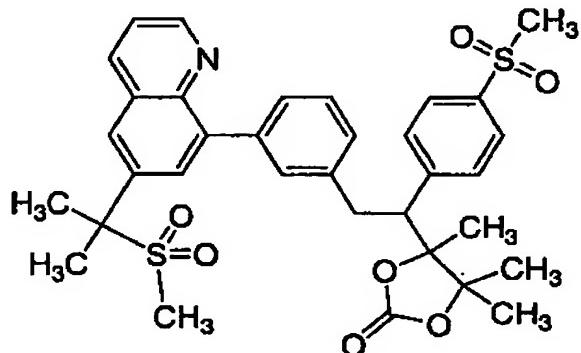
purification by flash chromatography (eluting with toluene/acetone, 9:1) afforded the title compound as a white foam. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/i-PrOH/EtOH, 3:1:1, retention time 30 and 43 min) to give Example 33A and Example 33B.

5 ¹H NMR (400MHz, acetone-d6): δ 8.89 (dd, 1H), 8.39 (dd, 1H), 8.21 (d, 1H), 7.92 (d, 1H), 7.83 (s, 4H), 7.52 (dd, 1H), 7.47 (s, 1H), 7.44 (dd, 1H), 7.18-7.16 (m, 2H), 3.94 (dd, 1H), 3.87 (dd, 1H), 3.69 (s, OH), 2.97 (s, 3H), 2.71 (s, 3H), 1.98 (s, 3H), 1.97 (s, 3H), 1.12-1.07 (m, 1H), 0.91-0.86 (m, 1H), 0.69-0.64 (m, 1H), 0.53-0.49 (m, 1H), 0.43-0.29 (m, 5H), 0.17-0.12 (m, 1H). LRMS (CI) 636 (M+H)⁺.

10

EXAMPLE 34

4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethyl]-4,5,5-trimethyl-[1,3]dioxolan-2-one



15

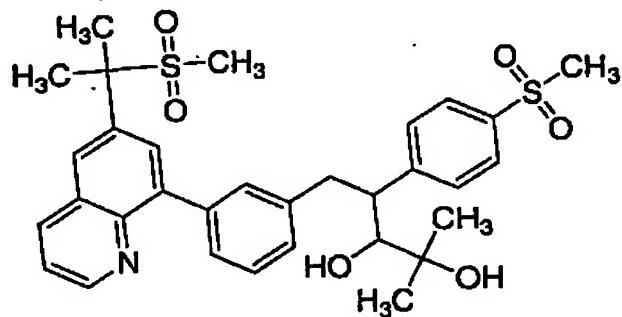
Example 10 (236mg, 0.39mmol) and CDI (650mg, 4mmol) was heated at 90°C for 18h, cooled to 21°C, and then diluted with ethyl acetate and sodium bicarbonate solution. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with dichloromethane / ethyl acetate, 40:60) provided the title compound as a white solid (245mg). The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/i-PrOH, 40:60, retention time 10.7 and 12.6 min) to give Example 34A and Example 34B.

¹H NMR (400MHz, acetone-d6): δ 8.89 (dd, 1H), 8.41 (dd, 1H), 8.21 (d, 1H), 7.95 (d, 1H), 7.86 (d, 2H), 7.78 (d, 2H), 7.59 (s, 1H), 7.54 (dd, 1H), 7.47 (d, 1H), 7.25 (t, 1H), 7.23 (d, 1H), 4.10 (dd, 1H), 3.47 (dd, 1H), 3.16 (dd, 1H), 3.06 (s, 3H), 2.71 (s, 3H), 1.96 (s, 6H), 1.87 (s, 3H), 1.71 (s, 3H), 1.48 (s, 3H).

5

EXAMPLE 35

5-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-4-(4-methanesulfonyl-phenyl)-2-methyl-pentane-2,3-diol



10

Following the procedures described above in Example 21, but substituting Example 1 for Example 6 and using THF/EtOH as solvent. Purification by flash chromatography (eluting with dichloromethane/ethyl acetate, 40:60) afforded the title compound (one pair of enantiomer).

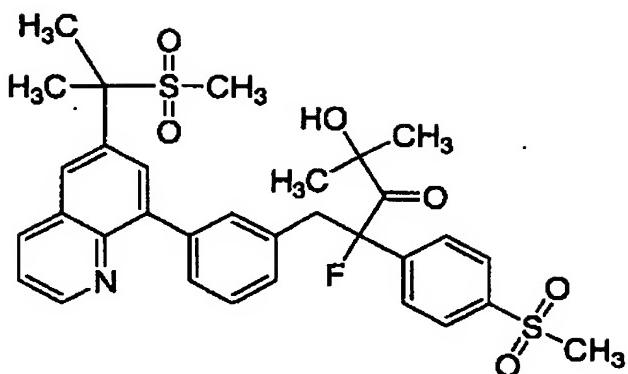
15

¹H NMR (400MHz, acetone-d6): δ 8.93 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.06 (d, 1H), 7.75 (dd, 4H), 7.60 (s, 1H), 7.56 (dd, 1H), 7.50 (d, 1H), 7.31 (t, 1H), 7.20 (d, 1H), 4.12 (d, 1H), 3.81 (m, 1H), 3.50 (m, 1H), 3.36 (dd, 1H), 3.26 (s, 1H), 3.10 (dd, 1H), 2.99 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H), 1.03 (s, 3H), 0.87 (s, 3H).

20

EXAMPLE 36

2-Fluoro-4-hydroxy-1-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-2-(4-methanesulfonyl-phenyl)-4-methyl-pentan-3-one



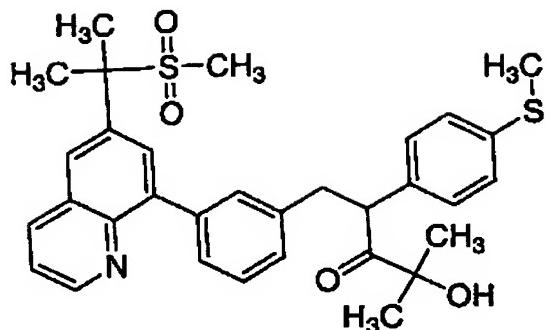
To a solution of Example 1 (200mg, 0.34mmol) in THF/DMF (1:1, 10mL) at 0°C was added potassium tert-butoxide (1M, THF, 0.34mL, 0.34mmol) dropwise. After 15 min, N-fluorobenzene sulfonimide (212mg, 0.73mmol) was added
 5 and the reaction mixture stirred for 2h at 21°C. The resulting mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 80:20) provided the title compound.

10 ¹H NMR (400MHz, acetone-d6): δ 8.93 (dd, 1H), 8.45 (dd, 1H), 8.29 (d, 1H), 8.08 (d, 1H), 7.98 (d, 2H), 7.88 (d, 2H), 7.55 (m, 3H), 7.38 (t, 1H), 7.26 (d, 1H), 4.22 (brs, 1H), 3.87 (dd, 1H), 3.42 (dd, 1H), 3.10 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H), 1.17 (s, 3H), 1.12 (s, 3H).

15

EXAMPLE 37

4-Hydroxy-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-methyl-2-(4-methylsulfanyl-phenyl)-pentan-3-one



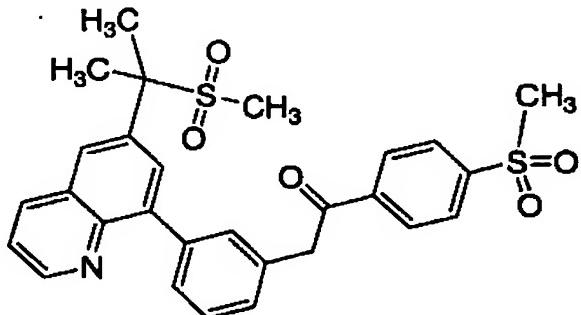
Following the procedures described in **Example 1**, but substituting **Ketone 01** for **Ketone 02** and purification by flash chromatography (eluting with ethyl acetate/hexane, 1:1 to 3:2) afforded the title compound as a white foam.

5 ¹H NMR (400MHz, acetone-d6): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.56 (dd, 1H), 7.51 (m, 2H), 7.33 (m, 3H), 7.2 (m, 3H), 4.94 (dd, 1H), 4.31 (s, OH), 3.38 (dd, 1H), 3.00 (dd, 1H), 2.7 (s, 3H), 2.44 (s, 3H), 1.98 (s, 6H), 1.07 (s, 3H), 1.03 (s, 3H).

10

EXAMPLE 38

2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanone



15 **Step 1:** (tert-Butyl-dimethyl-silyloxy)-(4-methylsulfanyl-phenyl)-acetonitrile

To a solution of 4-methylthiobenzaldehyde (8g, 52.5mmol) in acetonitrile (260mL) was added KCN (13.7g, 210mmol), ZnI₂ (335mg, 1mmol) and t-BDMSCl (9.5g, 63mmol). After 18h, the resulting reaction mixture was filtered and

the mother liquors concentrated. The resulting residue was left overnight under high vacuum to provided the (tert-butyl-dimethyl-silanyloxy)-(4-methylsulfanyl-phenyl)-acetonitrile compound as a clear oil.

5 **Step 2:** 2-(tert-Butyl-dimethyl-silanyloxy)-3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methylsulfanyl-phenyl)-propionitrile

To a solution of (tert-butyl-dimethyl-silanyloxy)-(4-methylsulfanyl-phenyl)-acetonitrile from **Step 1** above (1.52g, 5.2mmol) in THF (25mL) at -78°C was added KHMDS (1M, 5.2mL, 5.2mmol) dropwise followed, after 10 min, by

10 **Quinoline 01** (1.8g, 4.3mmol) in THF (25mL). The resulting reaction mixture was allowed to warm to -10°C and diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated.

15 **Step 3:** 2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methylsulfanyl-phenyl)-ethanone

To a solution of crude cyanohydrin from **Step 2** above in THF (25mL) was added tetrabutylammonium fluoride (1M, THF, 6.5mL, 6.5mmol) dropwise. The resulting reaction mixture was stirred at 21°C for 30min and diluted with a sodium hydroxide solution and ethyl acetate. The organic extracts were washed (1N NaOH 2 X), (brine), dried (MgSO₄), filtered and concentrated.

Step 4: 2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanone

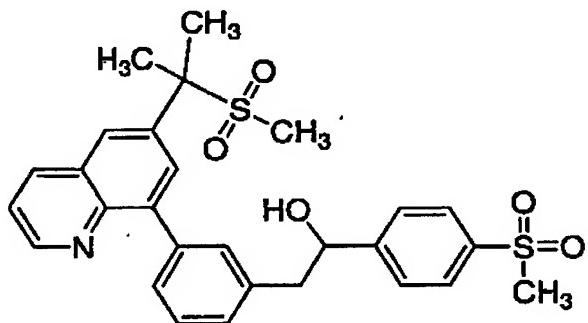
25 Following the procedures described above in **Example 16**, but substituting the 2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methylsulfanyl-phenyl)-ethanone from step 3 for **Example 15**, the 2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanone compound was obtained as a foam.

¹H NMR (400MHz, acetone-d₆): δ 8.89 (dd, 1H), 8.44 (dd, 1H), 8.35 (d, 2H), 8.26 (d, 1H), 8.10-8.08 (m, 3H), 7.72 (s, 1H), 7.63 (d, 2H), 7.56 (dd, 1H), 7.44 (t, 1H), 7.38 (d, 1H), 4.57 (s, 2H), 3.17 (s, 3H), 2.70 (s, 3H), 1.98 (s, 6H).

5

EXAMPLE 39

2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanol



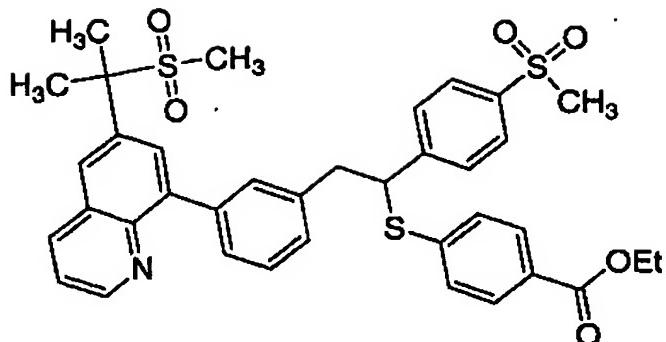
10 Following the procedures described above in Example 21, but substituting Example 38 for Example 6 and using THF/MeOH as solvent. The resulting residue was stirred vigorously in ethyl acetate/ether for 1h then filtered to afford the title compound as a white powder.

15 ¹H NMR (400MHz, acetone-d₆): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.09 (d, 1H), 7.88 (d, 2H), 7.61-7.53 (m, 3H), 7.59 (d, 2H), 7.36 (t, 1H), 7.27 (app d, 1H), 5.62 (app t, 1H), 4.67 (d, OH), 3.11 (d, 2H), 3.06 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H).

20

EXAMPLE 40

4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethylsulfanyl]-benzoic acid ethyl ester



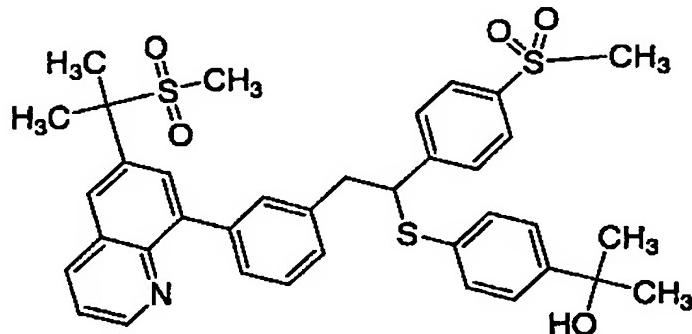
To a solution of Example 39 (283mg, 0.54mmol), Ph₃P (283mg, 1.08mmol) and DEAD (0.17mL, 1.08mmol) in THF (3mL) at 0°C, was slowly added ethyl 4-mercaptopbenzoate (200mg, 1.08mmol, over 20min.) in DMF (2mL). The reaction mixture was stirred at 0°C 1h, at 21°C for 18h, then diluted with water and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1) provided the title compound as an oil.

¹H NMR (400MHz, acetone-d₆): δ 8.92 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.05 (d, 1H), 7.85-7.81 (m, 4H), 7.74 (dd, 2H), 7.62 (s, 1H), 7.58-7.55 (m, 2H), 7.45 (dd, 2H), 7.32 (t, 1H), 7.23 (d, 1H), 5.13 (dd, 1H), 4.28 (q, 2H), 3.47-3.38 (m, 2H), 3.01 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H), 1.31 (t, 3H).

15

EXAMPLE 41

2-{4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethylsulfanyl]-phenyl}-propan-2-ol

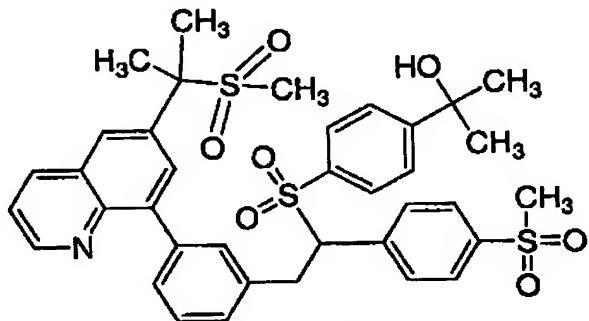


A solution of Example 40 (280mg, 0.4mmol) and anhydrous CeCl₃ (150mg, 0.5mmol) in THF (5mL) was stirred at 21°C for 1h, then cooled at -78°C. Methylmagnesium bromide (3M, Ether, 0.6mL, 2.1mmol) was added and the resulting reaction mixture warmed slowly to 0°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O), (brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1 to 2:8) provided the title compound as a solid.

5 ¹H NMR (400MHz, acetone-d₆): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.24
 10 (d, 1H), 8.04 (d, 1H), 7.79 (s, 2H), 7.71-7.53 (m, 5H), 7.41 (d, 2H), 7.32-7.28 (m,
 15 3H), 7.19 (d, 1H), 4.88 (dd, 1H), 4.02 (s, OH), 3.45-3.34 (m, 2H), 3.01 (s, 3H), 2.71
 20 (s, 3H), 1.97 (s, 6H), 1.44 (s, 6H).

EXAMPLE 42

15 2-{4-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonyl]-phenyl}-propan-2-ol



Following the procedures described above in Example 16, but substituting Example 41 for Example 15 and purification by stirring vigorously the resulting solid in hexane/ethyl acetate/ether for 1h and then filtration afforded the title compound as a white powder.

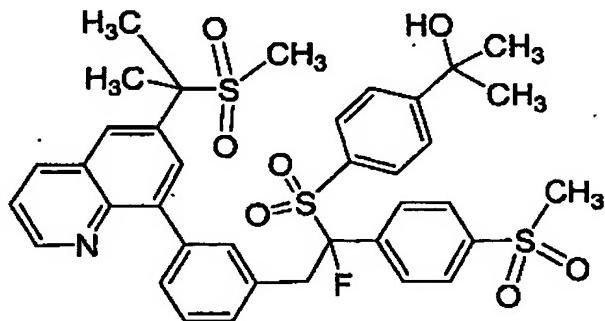
20 ¹H NMR (400MHz, acetone-d₆): δ 8.86 (dd, 1H), 8.41 (dd, 1H), 8.22
 25 (d, 1H), 7.93 (d, 1H), 7.79 (d, 2H), 7.71-7.51 (m, 8H), 7.71 (d, 1H), 7.47 (d, 1H), 7.24

(t, 1H), 5.07 (dd, 1H), 4.33 (s, OH), 3.75 (dd, 1H), 3.62 (dd, 1H), 3.05 (s, 3H), 2.70 (s, 3H), 1.95 (s, 6H), 1.50 (s, 3H), 1.50 (s, 3H).

5

EXAMPLE 43

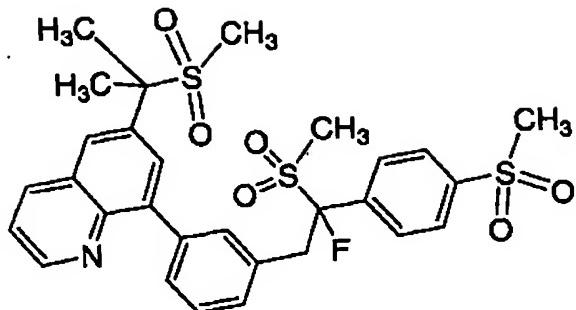
2-[4-[1-Fluoro-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonyl]-phenyl]-propan-2-ol



- By following the procedures described above in **Example 36**, but
10 substituting **Example 42** for **Example 1**, the title compound was obtained as a white solid.
- ¹H NMR (400MHz, acetone-*d*₆): δ 8.84 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.92 (d, 1H), 7.86 (d, 2H), 7.71-7.51 (m, 9H), 7.26 (t, 1H), 7.20 (d, 1H), 4.38 (s, OH), 4.19 (dd, 1H), 3.88 (dd, 1H), 3.07 (s, 3H), 2.69 (s, 3H), 1.96 (s, 3H), 1.94 (s, 3H), 1.51 (s, 3H), 1.50 (s, 3H).

EXAMPLE 44

8-[3-[2-Fluoro-2-methanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



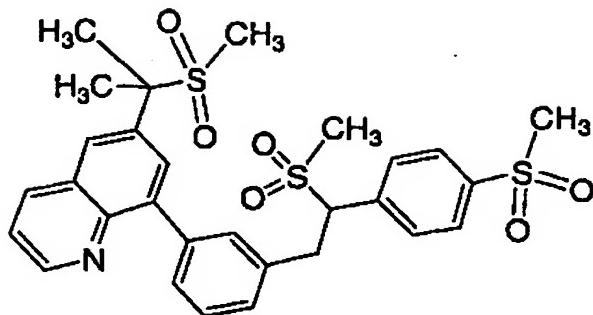
Example 44 was prepared by following the procedures described above in Example 1, but substituting Sulfone 02 for Ketone 02, and using DMF as solvent. Purification by flash chromatography (eluting with ethyl acetate/hexane, 95:5 to 100:0), then stirring vigorously the resulting solid in ether/ethyl acetate for 1h and filtration afforded the title compound as a white powder. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH/i-PrOH/MeOH, 30:30:30:10, retention time 10.0 and 12.5 min) to give Example 44A and Example 44B.

¹⁰ ¹H NMR (400MHz, ace-d6): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.85 (d, 2H), 7.57 (app d, 1H), 7.55 (dd, 1H), 7.50 (app d, 1H), 7.30 (t, 1H), 7.24 (app d, 1H), 5.01 (dd, 1H), 3.87 (dd, 1H), 3.55 (dd, 1H), 3.07 (s, 3H), 2.88 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

15

EXAMPLE 45

8-{3-[2-Methanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

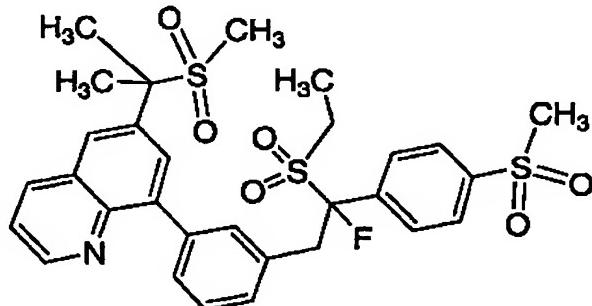


Example 45 was prepared by following the procedures described above in **Example 1**, but substituting **Sulfone 01** for **Ketone 02**, and using DMF as solvent. Purification by flash chromatography (eluting with ethyl acetate/hexane, 80:20 to 100:0), then stirring vigorously the resulting solid in ethyl acetate/ether for 1h and filtration afforded the title compound as a white powder.

¹H NMR (400MHz, acetone-*d*₆): δ 8.90 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.85 (d, 2H), 7.57 (app d, 1H), 7.55 (dd, 1H), 7.50 (d, 1H), 7.30 (t, 1H), 7.24 (d, 1H), 5.01 (dd, 1H), 3.87 (dd, 1H), 3.54 (dd, 1H), 3.07 (s, 3H), 2.88 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 46

15 **8-{3-[2-Ethanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**



Step 1: **8-{3-[2-Ethanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**

The procedures described above in Example 01 were followed, but Sulfone 04 was substituted for Ketone 02, and THF was used as the solvent. Purification by flash chromatography (eluting with ethyl acetate/hexane, 80:20 to 100:0), then stirring vigorously the resulting solid in ethyl acetate/ether for 1 h and 5 filtration afforded the 8-{3-[2-ethanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline compound as a white powder.

Step 2: 8-{3-[2-Ethanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

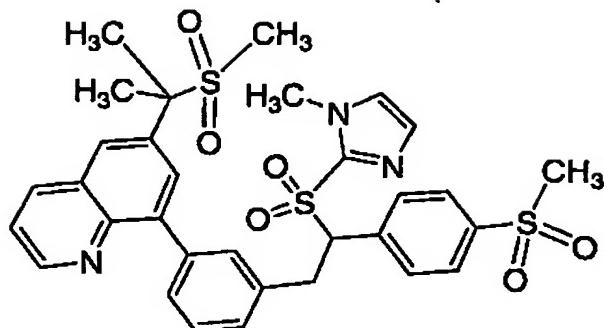
10 Following the procedures described in Example 36, but substituting 8-{3-[2-ethanesulfonyl-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline from Step 1 above for Example 1, the 8-{3-[2-ethanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline compound was obtained as a white solid.

15 ¹H NMR (400MHz, ace-d6): δ 8.89 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.01 (d, 2H), 7.96-7.92 (m, 3H), 7.57-7.53 (m, 3H), 7.29 (t, 1H), 7.21 (app d, 1H), 4.04 (m, 2H), 3.22-3.15 (m, 1H), 3.07 (s, 3H), 3.00-2.91 (m, 1H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H), 1.26 (t, 3H).

20

EXAMPLE 47

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[2-(4-methanesulfonyl-phenyl)-2-(1-methyl-1H-imidazole-2-sulfonyl)-ethyl]-phenyl}-quinoline

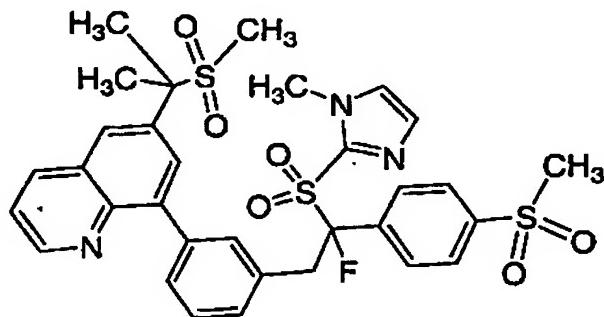


Example 47 was prepared by following the procedures described above in **Example 1**, but substituting **Sulfone 05** for **Ketone 02**, and using THF as solvent. Purification by flash chromatography (eluting with ethyl acetate), then stirring vigorously the resulting solid in ethyl acetate/ether for 1 h and filtration afforded the title compound as a white powder.

1 ¹H NMR (400MHz, ace-d6): δ 8.91 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.85 (d, 2H), 7.57 (d, 1H), 7.55 (dd, 1H), 7.50 (d, 1H), 7.30 (t, 1H), 7.24 (d, 1H), 5.01 (dd, 1H), 3.87 (dd, 1H), 3.55 (dd, 1H), 3.07 (s, 3H), 2.88 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H).

EXAMPLE 48

15 8-{3-[2-Fluoro-2-(4-methanesulfonyl-phenyl)-2-(1-methyl-1H-imidazole-2-sulfonyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



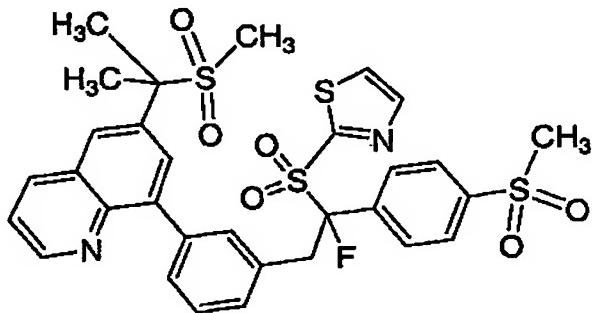
By following the procedures described above in **Example 36**, but substituting **Example 47** for **Example 1**, the title compound was obtained as a white solid.

5 ^1H NMR (400MHz, ace-*d*6): δ 8.85 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.97 (d, 2H), 7.93 (d, 1H), 7.77 (d, 1H), 7.55-7.52 (m, 3H), 7.49 (s, 1H), 7.27 (t, 1H), 7.21 (s, 1H), 7.19 (app d, 1H), 4.23 (d, 1H), 3.95 (dd, 1H), 3.79 (s, 3H), 3.11 (s, 3H), 2.70 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H).

10

EXAMPLE 49

8-{3-[2-Fluoro-2-(4-methanesulfonyl-phenyl)-2-(thiazole-2-sulfonyl)-ethyl]-phenyl}-6-(methanesulfonyl-1-methyl-ethyl)-quinoline

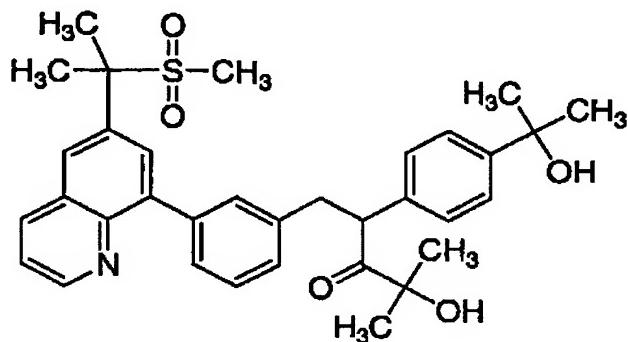


15 By following the procedures described above in **Example 46**, but substituting **Sulfone 06** for **Sulfone 04** in **Step 1**, the title compound was obtained as a white solid.

20 ^1H NMR (400MHz, ace-*d*6): δ 8.85 (dd, 1H), 8.41 (dd, 1H), 8.31 (d, 1H), 8.22 (d, 1H), 8.20 (d, 1H), 7.97-7.93 (m, 3H), 7.82 (d, 2H), 7.56-7.52 (m, 3H), 7.28 (t, 1H), 7.21 (app d, 1H), 4.30 (dd, 1H), 4.10 (dd, 1H), 3.09 (s, 3H), 2.70 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H).

EXAMPLE 50

4-Hydroxy-2-[4-(1-hydroxy-1-methyl-ethyl)-phenyl]-1-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-4-methyl-pentan-3-one

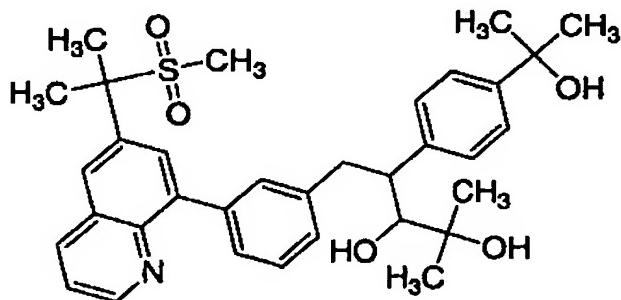


5 By following the procedures described above in **Example 1**, but substituting **Ketone 11** for **Ketone 02**, the title compound was obtained as a white foam.

10 ^1H NMR (400MHz, acetone-*d*6): δ 8.93 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.07 (d, 1H), 7.58 (m, 2H), 7.49 (d, 1H), 7.45 (d, 2H), 7.35 (m, 3H), 7.22 (d, 1H), 4.97 (dd, 1H), 4.27 (s, OH), 3.94 (s, OH), 3.38 (dd, 1H), 2.99 (dd, 1H), 2.71 (s, 3H), 1.99 (s, 6H), 1.46 (s, 6H), 1.04 (s, 3H), 1.00 (s, 3H).

EXAMPLE 51

15 **4-[4-(1-Hydroxy-1-methyl-ethyl)-phenyl]-5-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-methyl-pentane-2,3-diol**



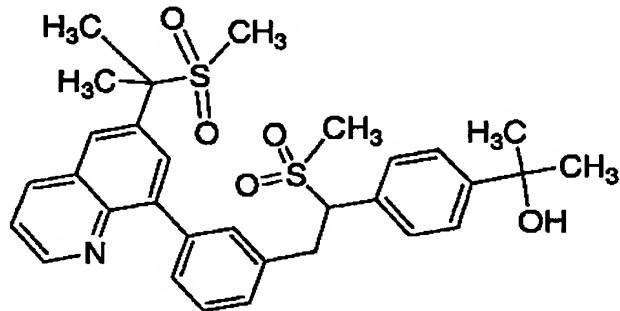
By following the procedures described above in **Example 21**, but substituting **Example 50** for **Example 6** and using EtOH as solvent, the title compound was obtained as a white foam.

5 ^1H NMR (400MHz, acetone-*d*6): δ 8.93 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.09 (d, 1H), 7.65 (s, 1H), 7.56 (dd, 1H), 7.52 (d, 1H), 7.45-7.32 (m, 4H), 7.32 (t, 1H), 7.23 (d, 1H), 3.86 (s, OH), 3.71 (m, 2H), 3.30 (m, 2H), 3.01 (m, 2H), 2.71 (s, 3H), 1.99 (s, 6H), 1.45 (s, 6H), 1.05 (s, 3H), 0.78 (s, 3H).

10

EXAMPLE 52

2-[4-(1-Methanesulfonyl-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-ethyl)-phenyl]-propan-2-ol

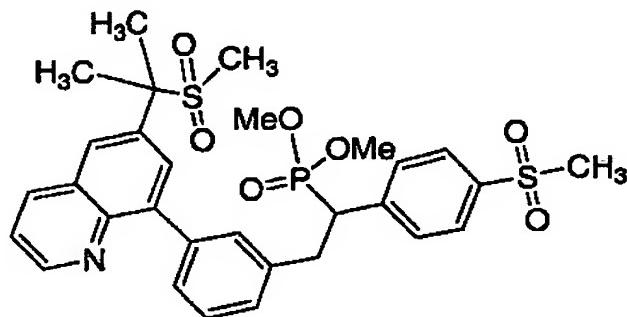


15 By following the procedures described above in **Example 1**, but substituting **Sulfone 07** for **Ketone 02**, the title compound was obtained as a white foam.

19 ^1H NMR (400MHz, acetone-*d*6): δ 8.90 (dd, 2H), 8.42 (dd, 2H), 8.24 (d, 1H), 8.00 (d, 1H), 7.59 (s, 1H), 7.55 (dd, 1H), 7.51 (m, 5H), 7.29 (t, 1H), 7.21 (d, 1H), 4.75 (dd, 1H), 3.99 (s, OH), 3.81 (dd,), 3.49 (dd, 1H), 2.74 (s, 3H), 2.7 (s, 3H), 20 1.97 (s, 6H), 1.44 (s, 6H).

EXAMPLE 53

[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethyl]-phosphonic acid dimethyl ester



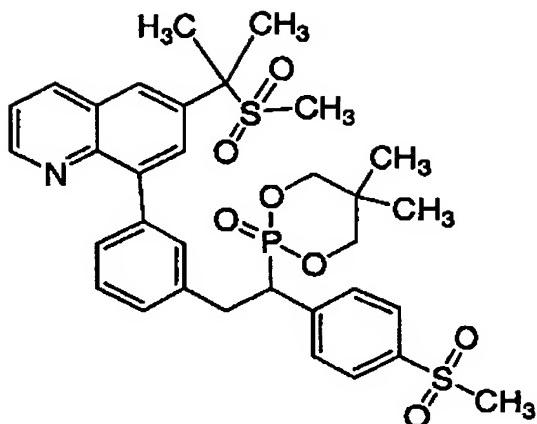
By following the procedures described above in **Example 1**, but

- 5 substituting **Phosphonate 01** for **Ketone 02** and purification by flash chromatography (eluting with toluene/acetone, 50:50), the title compound was obtained as a white foam.

¹H NMR (400MHz, acetone-d6): δ 8.89 (dd, 1H), 8.40 (dd, 1H), 8.23 (d, 1H), 8.01 (d, 1H), 7.84 (d, 2H), 7.71 (d, 2H), 7.50 (m, 3H), 7.26 (s, 1H), 7.19 (d, 1H), 3.90 (m, 1H), 3.71 (d, 3H), 3.57 (d, 3H), 3.55 (m, 1H), 3.40 (m, 1H), 3.02 (s, 3H), 2.70 (s, 3H), 1.98 (s, 6H).

EXAMPLE 54

- 15 **8-{3-[2-(5,5-Dimethyl-2-oxo-2λ⁵-[1,3,2]dioxaphosphinan-2-yl)-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline**



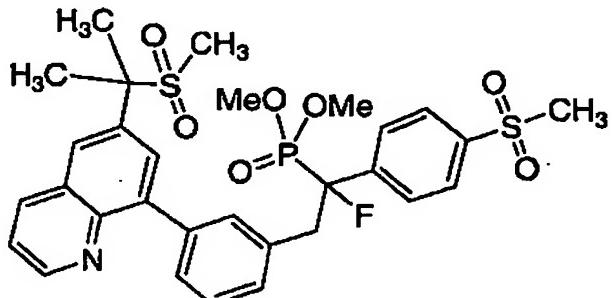
By following the procedures described above in **Example 1**, but substituting **Phosphonate 03** for **Ketone 02** and purification by flash chromatography (eluting with toluene/acetone, 60:40), the title compound was obtained as a white 5 foam.

¹H NMR (400MHz, acetone-d6): δ 8.90 (dd, 1H), 8.42 (dd, 1H), 8.24 (d, 1H), 8.00 (d, 1H), 7.84 (d, 2H), 7.73 (d, 2H), 7.53 (m, 3H), 7.27 (t, 1H), 7.18 (d, 1H), 4.20 (m, 3H), 4.03 (m, 1H), 3.92 (m, 1H), 3.57 (m, 1H), 3.40 (m, 1H), 3.06 (s, 3H), 2.72 (s, 3H), 1.97 (s, 6H), 1.13 (s, 3H), 0.91 (s, 3H).

10

EXAMPLE 55

[1-Fluoro-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethyl]-phosphonic acid dimethyl ester



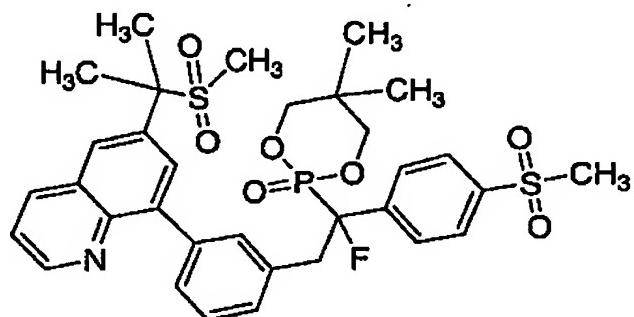
15

By following the procedures described above in Example 1, but substituting **Phosphonate 02** for **Ketone 02** and purification by flash chromatography (eluting with toluene/acetone, 60:40), the title compound was obtained as a white foam.⁵⁴ corrected ¹H NMR (400MHz, acetone-d₆): δ 8.88 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.96 (d, 1H), 7.92 (d, 2H), 7.78 (d, 2H), 7.53 (m, 2H), 7.49 (s, 1H), 7.28 (t, 1H), 7.14 (s, 1H), 3.84 (d, 3H), 3.83 (m, 2H), 3.58 (d, 3H), 3.02 (s, 3H), 2.70 (s, 3H), 1.97 (s, 3H), 1.96 (s, 3H).

10

EXAMPLE 56

8-{3-[2-(5,5-Dimethyl-2-oxo-2λ⁵-[1,3,2]dioxaphosphinan-2-yl)-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



15

By following the procedures described above in Example 36, but substituting Example 54 for Example 1 and purification by flash chromatography (eluting with toluene/acetone, 75:25), the title compound was obtained as a white foam.

20

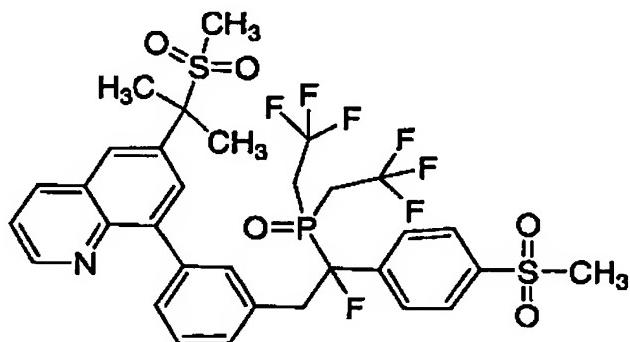
¹H NMR (400MHz, acetone-d₆): δ 8.90 (dd, 1H), 8.41 (dd, 1H), 8.22 (d, 1H), 7.98 (d, 1H), 7.93 (d, 2H), 7.80 (d, 2H), 7.53 (m, 2H), 7.48 (s, 1H), 7.26 (t, 1H), 7.14 (d, 1H), 4.53 (dd, 1H), 4.38 (dd, 1H), 4.14 (m, 1H), 3.96 (m, 1H), 3.89 (m, 1H), 3.72 (m, 1H), 3.02 (s, 3H), 2.70 (s, 3H), 1.97 (s, 6H), 1.25 (s, 3H), 0.93 (s, 3H).

25

EXAMPLE 57

- - - o o o o

8-[3-[2-[Bis-(2,2,2-trifluoro-ethyl)-phosphinoyl]-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline

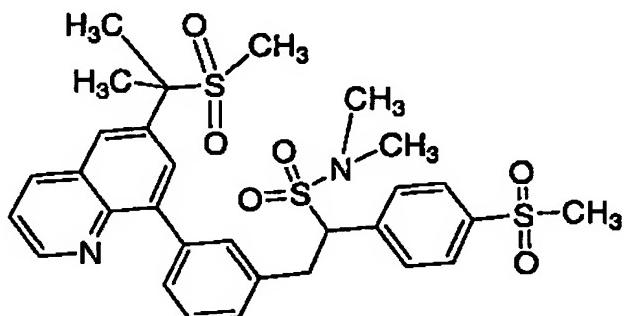


Following the procedures described above in **Example 46**, but
 5 substituting **Phosphonate 04** for **Sulfone 04** and purification by flash chromatography (eluting with toluene/acetone, 70:30), afforded the title compound as a white foam.

¹H NMR (400MHz, acetone-d6): δ 8.90 (dd, 1H), 8.45 (m, 1H), 8.29 (m, 1H), 8.25 (d, 1H), 8.10 (d, 1H), 7.95 (d, 2H), 7.85 (d, 1H), 7.59 (m, 3H), 7.33 (t, 1H), 7.27 (d, 1H), 4.78 (m, 1H), 4.59 (m, 2H), 4.39 (m, 1H), 3.85 (m, 2H), 3.05 (s, 3H), 2.71 (s, 3H), 1.98 (s, 6H).

EXAMPLE 58

15 **2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonic acid dimethylamide**



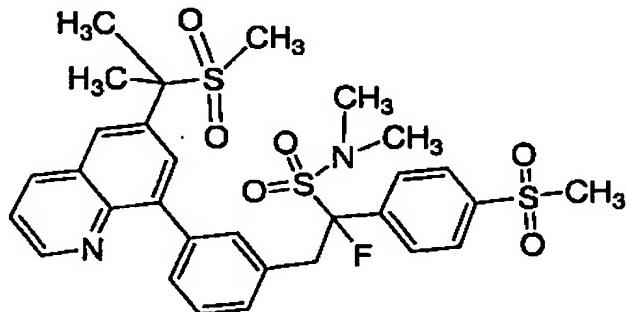
By following the procedures described above in **Example 1**, but substituting **Sulfone 08** for **Ketone 02**, the title compound was obtained as a white foam.

¹H NMR (400MHz, acetone-d₆): δ 8.88 (dd, 1H), 8.39 (dd, 1H), 8.22 (d, 1H), 7.97 (d, 1H), 7.93 (d, 2H), 7.86 (d, 2H), 7.55-7.50 (m, 3H), 7.29-7.19 (m, 2H), 5.03 (dd, 1H), 3.75 (dd, 1H), 3.57 (dd, 1H), 3.05 (s, 3H), 2.70 (s, 3H), 2.67 (s, 6H), 1.96 (s, 6H).

10

EXAMPLE 59

1-Fluoro-2-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-ethanesulfonic acid dimethylamide

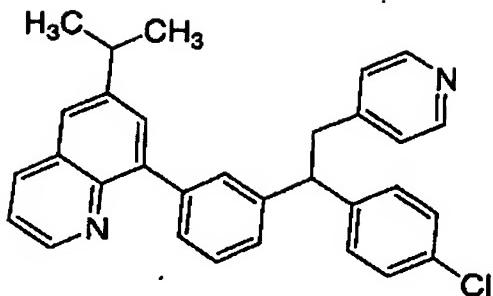


15 By following the procedures described above in **Example 36**, but substituting **Example 58** for **Example 1**, the title compound was obtained as a white solid.

¹H NMR (400MHz, acetone-d₆): δ 8.98 (d, 1H), 8.88 (dd, 1H), 8.18 (dd, 1H), 7.90 (d, 2H), 7.81 (d, 3H), 7.48 (d, 1H), 7.41 (dd, 1H), 7.39 (s, 1H), 7.25 (t, 1H), 7.07 (d, 1H), 3.96-3.80 (m, 2H), 2.95 (s, 3H), 2.68 (br s, 6H), 2.60 (s, 3H), 1.944 (s, 3H), 1.936 (s, 3H).

EXAMPLE 60

8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-isopropyl-quinoline



Step 1: (4-Chloro-phenyl)-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol

To a solution of **Quinoline 04** (1.0g, 3.6mmol) in CH₂Cl₂ (5mL) at -10°C was added 4-chlorophenylmagnesium bromide (0.7M, THF, 5mL, 7mmol) dropwise. After 1h, a saturated ammonium chloride solution was added and the reaction mixture extracted with CH₂Cl₂ (3X). The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the (4-chloro-phenyl)-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol compound as a white solid.

10

Step 2: 8-{3-[Chloro-(4-chloro-phenyl)-methyl]-phenyl}-6-isopropyl-quinoline

To a solution of (4-chloro-phenyl)-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol from **Step 1** (1.0g, 2.58mmol) in benzene (7mL) at 0°C was added SOCl₂ (0.375mL, 5.2mmol) dropwise. After 45min. at 0-10°C, the resulting reaction mixture was filtered through silica gel and celite and then concentrated.

Step 3: 3-(4-Chloro-phenyl)-3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionic acid ethyl ester

To a solution of ethyl 4-pyridinylacetate (1.28g, 7.74mmol) in THF/HMPA (3:1, 5mL) at -10°C was added NaHMDS (1M, 7.8mL, 7.8mmol) dropwise. After 60min., the crude chloride from **Step 2** above was added and the resulting reaction mixture was stirred for 18h at 21°C, and then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated.

Step 4: 8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-isopropyl-quinoline

To a solution of the crude ester from Step 3 above in THF/EtOH

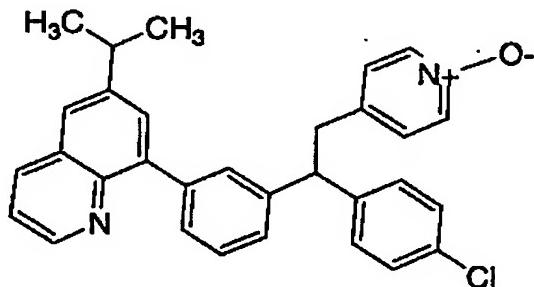
- 5 (10mL) was added NaOH (2N, 2mL). The resulting reaction mixture was stirred 18h at 100°C then neutralized with HCl 6N to pH 7 and diluted with ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1) provided the 8-{3-[1-(4-chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-isopropyl-quinoline
10 compound.

¹H NMR (500MHz, acetone-d6): δ 8.81 (dd, 1H), 8.36 (d, 2H), 8.30 (dd, 1H), 7.76 (d, 2H), 7.6 (s, 1H), 7.51 (d, 1H), 7.46 (m, 3H), 7.33 (m, 4H), 7.22 (d, 2H), 4.53 (t, 1H), 3.52 (m, 2H), 3.15 (m, 1H), 1.39 (s, 6H).

15

EXAMPLE 61

8-{3-[1-(4-Chloro-phenyl)-2-(1-oxy-pyridin-4-yl)-ethyl]-phenyl}-6-isopropyl-quinoline



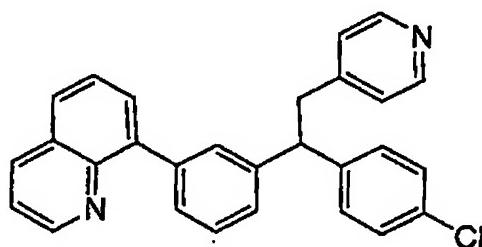
- 20 To a solution of Example 60 (100mg, 0.22mmol) in CH₂Cl₂/MeOH (1:1, 6mL) was added MMPP (320mg, 0.65mmol). After 18h, the resulting reaction mixture was diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with ethanol/ethyl acetate, 10:90 to
25 25:75) provided the title compound.

¹H NMR (500MHz, acetone-d₆): δ 8.83 (dd, 1H), 8.30 (dd, 1H), 7.95 (d, 2H), 7.76 (d, 2H), 7.63 (s, 1H), 7.48 (m, 4H), 7.35 (m, 4H), 7.22 (d, 2H), 4.49 (t, 1H), 3.52 (m, 2H), 3.18 (m, 1H), 1.39 (s, 6H).

5

EXAMPLE 62

8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-quinoline



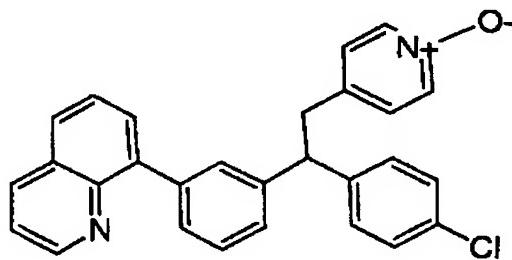
- 10 **Step 1:** 4-[2-(3-Bromo-phenyl)-2-(4-chloro-phenyl)-ethyl]-pyridine
 Following the procedures described above in Example 60, but substituting 3-bromobenzaldehyde for Quinoline 04 and purification by flash chromatography (eluting with hexane/ethyl acetate, 4:1) afforded the 4-[2-(3-bromo-phenyl)-2-(4-chloro-phenyl)-ethyl]-pyridine compound.
- 15 **Step 2:** 8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-quinoline
 A solution of 4-[2-(3-bromo-phenyl)-2-(4-chloro-phenyl)-ethyl]-pyridine from Step 1 above (400mg, 1.07mmol), diboron pinacol ester (300mg, 1.18mmol), KOAc (315mg, 3.2mmol) and PdCl₂(dpff) (26mg, 0.032mmol) in DMF (20mL) was heated at 80°C under N₂ for 5h. The resulting reaction mixture was cooled to 21°C, 8-bromoquinoline (290mg, 1.4mmol), Na₂CO₃ (2M, 1.61mL, 3.2mmol) and PdCl₂(dpff) (26mg, 0.032mmol) was then added. The reaction mixture was stirred 18h at 80°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50 to 25:75) provided the 8-{3-[1-(4-chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-quinoline compound (319mg).

¹H NMR (500MHz, acetone-d₆): δ 8.88 (dd, 1H), 8.37(d, 1H), 8.36(d, 2H), 7.95 (dd, 1H), 7.76 (s, 1H), 7.71 (dd, 1H), 7.64 (t, 1H), 7.52 (m, 2H), 7.48 (d, 2H), 7.37 (d, 2H), 7.28 (d, 2H), 7.21 (d, 2H), 4.51 (t, 1H), 3.52 (m, 2H).

5

EXAMPLE 63

8-{3-[1-(4-Chloro-phenyl)-2-(1-oxy-pyridin-4-yl)-ethyl]-phenyl}-quinoline



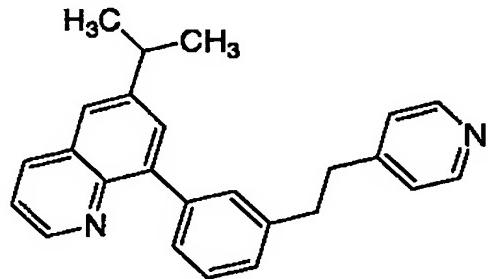
Following the procedures described above in Example 61, but
10 substituting Example 62 for Example 60, the title compound was obtained.

¹H NMR (500MHz, acetone-d₆): δ 8.90 (dd, 1H), 8.38(dd, 1H), 7.94(m, 3H), 7.72 (t, 2H), 7.65 (t, 1H), 7.52 (m, 2H), 7.48(d, 2H), 7.32 (m, 4H), 7.21 (d, 2H), 4.48 (t, 1H), 3.50 (m, 2H).

15

EXAMPLE 64

6-Isopropyl-8-[3-(2-pyridin-4-yl-ethyl)-phenyl]-quinoline

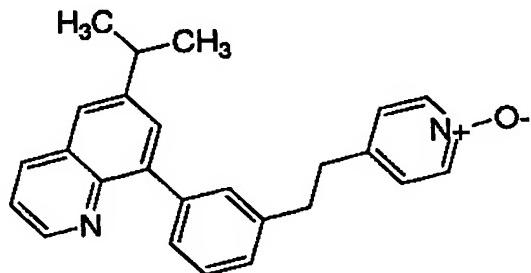


Using 3-bromobenzyl chloride as the starting material, and following the procedures described above in **Example 60, Steps 3 and 4**, followed by procedures described in **Example 62, Step 2**, the title compound was obtained.

¹H NMR (300MHz, acetone-d6): δ 8.80 (dd, 1H), 8.44 (dd, 2H), 8.29
 5 (dd, 1H), 7.76 (d, 1H), 7.63 (d, 1H), 7.52 (s, 2H), 7.46 (q, 1H), 7.25 (t, 1H), 7.25 (d,
 3H), 3.16 (m, 1H), 3.01 (s, 4H), 1.38 (d, 6H).

EXAMPLE 65

10 6-Isopropyl-8-{3-[2-(1-oxy-pyridin-4-yl)-ethyl]-phenyl}-quinoline

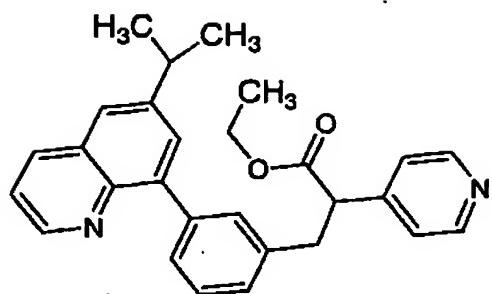


Following the procedures described in **Example 61**, but substituting **Example 64** for **Example 60**, the title compound was obtained.

¹H NMR (500MHz, acetone-d6): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 8.01
 15 (d, 2H), 7.76 (d, 1H), 7.65 (d, 1H), 7.52 (s&dd, 2H), 7.48 (q, 1H), 7.36 (t, 1H), 7.24
 (d, 3H), 3.17 (m, 1H), 3.01 (s, 4H), 1.36 (s, 6H).

EXAMPLE 66

20 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionic acid ethyl ester



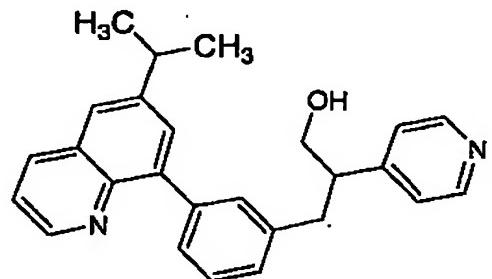
Using 3-bromobenzyl chloride as the starting material, and following the procedures described in **Example 60, Step 3**, followed by procedures described in **Example 62, Step 2**, the title compound was obtained as an oil.

5 ¹H NMR (500MHz, acetone-d6): δ 8.82 (s, 1H), 8.52 (d, 2H), 8.28 (dd, 1H), 7.78 (d, 1H), 7.58 (d, 2H), 7.49 (t, 2H), 7.38 (m, 3H), 7.21 (d, 1H), 4.05 (q, 1H), 3.48 (q, 2H), 3.1 (q, 2H), 1.38 (d, 6H), 1.1 (t, 3H).

10

EXAMPLE 67

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propan-1-ol



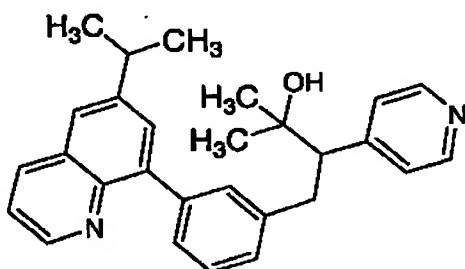
To a solution of **Example 66** (15mg, 0.035mmol) in THF (mL) at 0°C was added LiAlH₄ (1M, THF, 0.35mL, 0.35mmol) dropwise. The resulting reaction 15 mixture was stirred 1h at 0°C, 1h at 21°C, and then quenched with water and neutralized using 1N HCl. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with ethanol/ethyl acetate, 1:9) provided the title compound.

¹H NMR (400MHz, acetone-*d*6): δ 8.78 (dd, 1H), 8.33 (dd, 1H), 7.76 (d, 1H), 7.49 (q, 1H), 7.45 (d, 1H), 7.42 (d, 1H), 7.29 (t, 4H), 7.13 (d, 1H), 4.78 (t, 1H), 3.6 (m, 2H), 3.16 (m, 3H), 2.92 (q, 1H), 1.31 (s, 6H).

5

EXAMPLE 68

4-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-butan-2-ol

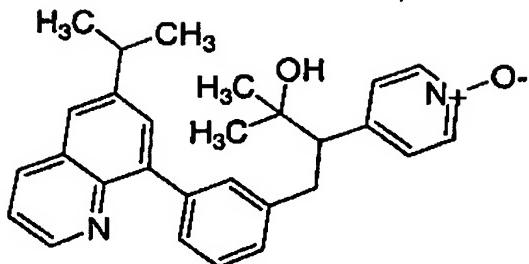


- To a solution of Example 66 (750mg, 1.77mmol) in THF (40mL) at
 10 0°C was added methylmagnesium iodide (3M, THF, 12mL, 35mmol) dropwise. The reaction mixture was stirred 3h at 0°C, then quenched with a saturated ammonium chloride solution. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1) provided the title compound.
- 15 ¹H NMR (400MHz, acetone-*d*6): δ 8.77 (dd, 1H), 8.39 (dd, 2H), 8.27 (dd, 1H), 7.71 (d, 1H), 7.45 (q, 1H), 7.41 (d, 2H), 7.30 (d, 3H), 7.18 (t, 1H), 7.08 (d, 1H), 3.73 (s, 1H), 3.51 (dd, 1H), 3.16 (m, 2H), 3.03 (dd, 1H), 1.36 (d, 6H), 1.28 (s, 3H), 1.19 (s, 3H).

20

EXAMPLE 69

4-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-(1-oxy-pyridin-4-yl)-butan-2-ol

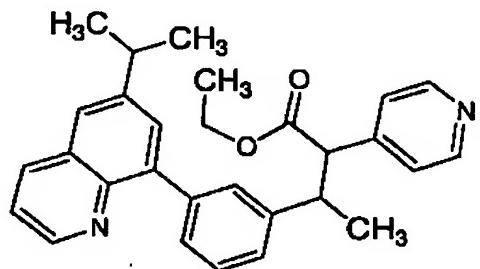


Following the procedures described in **Example 61**, but substituting **Example 68** for **Example 60**, the title compound was obtained.

- 15 ^1H NMR (400MHz, acetone-*d*₆): δ 8.82 (dd, 1H), 8.27 (dd, 1H), 7.96
 (d, 2H), 7.73 (dd, 1H), 7.51 (d, 1H), 7.44 (q, 1H), 7.38 (m, 2H), 7.31 (d, 2H), 7.22 (t,
 1H), 7.09 (d, 1H), 3.84 (s, 1H), 3.48 (d, 1H), 3.15 (m, 3H), 1.36 (t, 9H), 1.18 (s, 3H).

EXAMPLE 70

- 10 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-butyric acid ethyl ester

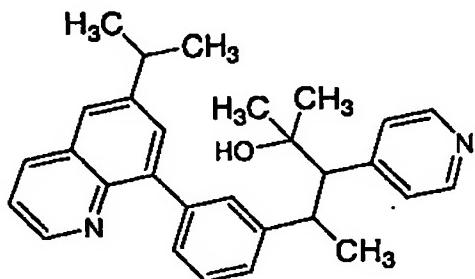


Following the procedures described in **Example 60**, Steps 1-3, but substituting methylmagnesium iodide for 4-chlorophenylmagnesium bromide, the title compound was obtained as a mixture of diastereoisomer.

- 15 ^1H NMR (500MHz, acetone-*d*₆): δ 8.83 (dd, 1H), 8.36 (dd, 2H), 8.26
 (dd, 1H), 7.72 (d, 1H), 7.42 (m, 4H), 7.31 (dd, 2H), 7.22 (t, 1H), 7.13 (d, 1H), 4.21
 (m, 3H), 3.95 (d, 1H), 3.58 (m, 1H), 3.12 (m, 1H), 1.48 (d, 3H), 1.36 (d, 6H), 1.18 (t,
 2H).

EXAMPLE 71

4-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-pentan-2-ol

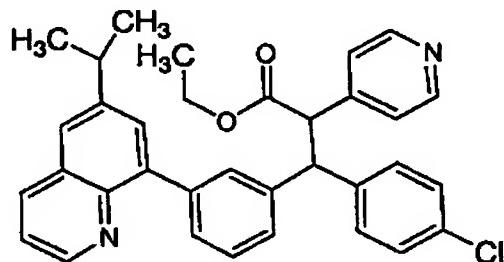


Following the procedures described in **Example 68**, but substituting
5 Example 70 for Example 66, the title compound was obtained as a mixture of
diastereoisomers.

10 ¹H NMR (400MHz, acetone-*d*6): δ 8.83 (dd, 1H), 8.34 (dd, 2H), 8.27
(dd, 1H), 7.79 (d, 1H), 7.49 (m, 2H), 7.42 (d, 1H), 7.38 (dd, 2H), 7.28 (dd, 2H), 7.18
(d, 1H), 4.39 (s, 1H), 3.58 (m, 1H), 3.12 (m, 1H), 2.88 (d, 1H), 1.35 (d, 6H), 1.21 (s,
3H), 1.05 (d, 3H), 0.9 (s, 3H).

EXAMPLE 72

15 **4-(4-Chloro-phenyl)-4-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-butан-2-ol**



Following the procedures described in **Example 60, Steps 1-3**, the title
compound was obtained as a mixture of diastereoisomers.

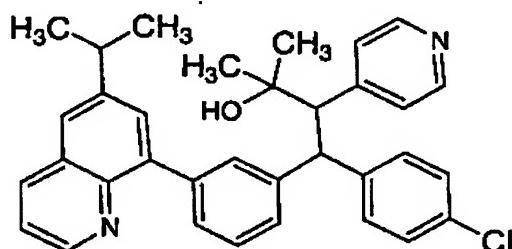
Isomer A: ^1H NMR (400MHz, acetone-*d*6): δ 8.81 (dd, 1H), 8.48 (d, 2H), 8.31 (dd, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.58 (d, 1H), 7.52 (d, 1H), 7.48 (q, 1H), 7.41 (m, 6H), 7.18 (d, 1H), 4.92 (d, 1H), 4.81 (d, 1H), 4.02 (m, 2H), 3.12 (m, 1H), 1.39 (d, 6H), 0.92 (t, 3H).

5 Isomer B: ^1H NMR (500MHz, acetone-*d*6): δ 8.81 (dd, 1H), 8.48 (d, 1H), 8.42 (dd, 1H), 8.31 (m, 2H), 7.72 (d, 1H), 7.68 (d, 1H), 7.62 (d, 1H), 7.52 (d, 2H), 7.43 (m, 3H), 7.35 (d, 2H), 7.21 (t, 1H), 7.15 (d, 1H), 4.95 (d, 1H), 4.78 (d, 1H), 3.98 (m, 2H), 3.11 (m, 1H), 1.37(d, 6H), 0.95 (t, 3H).

10

EXAMPLE 73

4-(4-Chloro-phenyl)-4-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-methyl-3-pyridin-4-yl-butan-2-ol



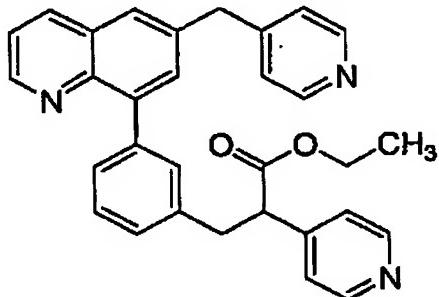
15

Following the procedures described in Example 68, but substituting Example 72 for Example 66, the title compound was obtained as a mixture of diastereoisomer.

^1H NMR (400MHz, acetone-*d*6): δ 8.81 (dd, 1H), 8.48 (d, 2H), 8.31 (dd, 1H), 7.92 (s, 1H), 7.78 (s, 1H), 7.68 (s, 1H), 7.58 (d, 1H), 7.52 (d, 1H), 7.48 (q, 1H), 7.41 (m, 6H), 7.18 (d, 1H), 5.0(d, 1H), 4.02 (d, 1H), 3.15(m, 1H), 1.38(m 9H), 1.1(t, 3H).

EXAMPLE 74

2-Pyridin-4-yl-3-[3-(6-pyridin-4-ylmethyl-quinolin-8-yl)-phenyl]-propionic acid ethyl ester

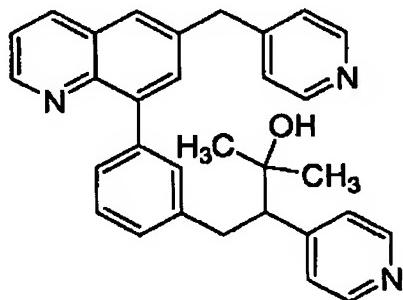


Using procedures described in **Example 60, Step 3**, but using 3-
5 bromobenzyl chloride as the starting material, followed by the procedures described in
Example 62, Step 2, but substituting 8-bromo 6-[(4-pyridinyl)methyl]quinoline for 8-
bromoquinoline, the title compound was obtained as a oil.

¹H NMR (500MHz, acetone-d6): δ 8.82 (dd, 1H), 8.46 (q, 4H), 8.30
(dd, 1H), 7.81 (s, 1H), 7.50 (s, 1H), 7.48 (m, 2H), 7.44 (s, 1H), 7.34 (m, 5H), 7.22 (d,
10 1H), 4.25 (s, 2H), 4.05 (m, 3H), 3.44 (dd, 1H), 3.13 (dd, 1H), 1.07 (t, 3H).

EXAMPLE 75

2-Methyl-3-pyridin-4-yl-4-[3-(6-pyridin-4-ylmethyl-quinolin-8-yl)-phenyl]-
15 butan-2-ol



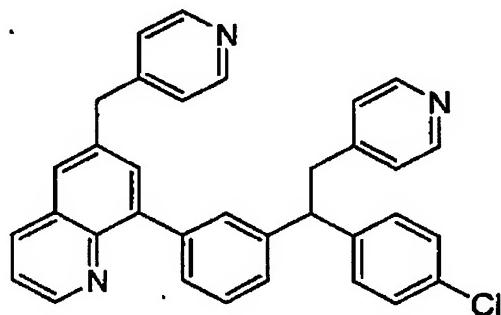
Following the procedures described in **Example 68**, but substituting
Example 74 for **Example 66**, the title compound was obtained.

¹H NMR (400MHz, acetone-*d*6): δ 8.81 (dd, 1H), 8.48 (dd, 2H), 8.36 (dd, 2H), 8.27 (dd, 1H), 7.76 (d, 1H), 7.48 (q, 1H), 7.34 (m, 5H), 7.28 (d, 2H), 7.18 (t, 1H), 7.05 (d, 1H), 4.23 (s, 2H), 3.48 (dd, 1H), 3.11 (m, 2H), 1.32 (s, 3H), 1.14 (s, 3H).

5

EXAMPLE 76

8-{3-[1-(4-Chloro-phenyl)-2-pyridin-4-yl-ethyl]-phenyl}-6-pyridin-4-ylmethyl-quinoline



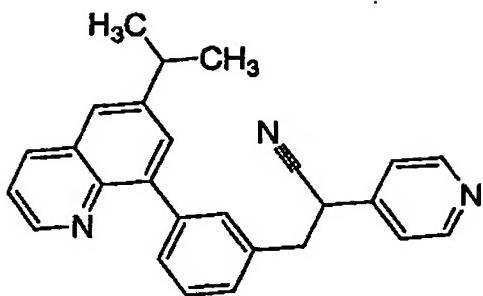
10 Following the procedures described in Example 62, but substituting 8-bromo-6-pyridin-4-ylmethyl-quinoline for 8-bromoquinoline and purification by flash chromatography (eluting with ethyl acetate/EtOH, 10:0 to 9:1) afforded the title compound.

15 ¹H NMR (500MHz, acetone-*d*6): δ 8.84 (dd, 1H), 8.48 (dd, 2H), 8.35 (dd, 2H), 8.29 (dd, 1H), 7.81 (d, 1H), 7.68 (s, 1H), 7.51 (d, 1H), 7.45 (m, 2H), 7.40 (d, 2H), 7.32 (dd, 4H), 7.27 (d, 2H), 7.20 (dd, 2H), 4.50 (t, 1H), 4.24 (s, 2H), 3.47 (m, 2H).

20

EXAMPLE 77

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionitrile



Step 1: 3-(3-Bromo-phenyl)-2-pyridin-4-yl-propionitrile

The procedures described in **Example 60, Step 3**, were followed but substituting 4-pyridinylacetonitrile for ethyl 4-pyridinylacetate and using 3-bromobenzyl chloride as the starting material.

Step 2: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionitrile

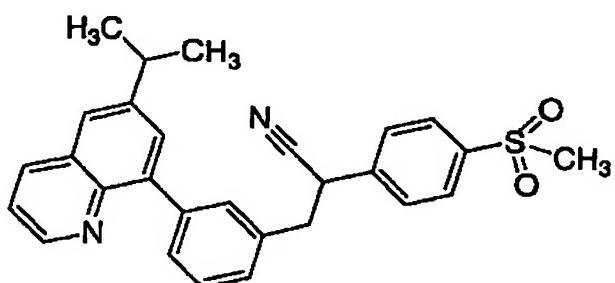
Following the procedures described in **Example 62, Step 2**, but substituting 8-bromo-6-isopropylquinoline for 8-bromoquinoline and purification by flash chromatography (eluting with ethylacetate/hexane, 75:25) afforded the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-propionitrile compound.

¹H NMR (500MHz, acetone-d6): δ 8.81 (dd, 1H), 8.60 (dd, 2H), 8.30 (dd, 1H), 7.76 (d, 1H), 7.65 (d, 1H), 7.60 (d, 1H), 7.54 (s, 1H), 7.47 (q, 1H), 7.43 (dd, 2H), 7.39 (t, 1H), 7.29 (d, 1H), 4.56 (t, 1H), 3.36 (d, 2H), 3.16 (m, 1H), 1.37 (s, 6H).

15

EXAMPLE 78

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionitrile



20 **Step 1: (4-Methanesulfonyl-phenyl)-acetonitrile**

To a solution of 4-methanesulfonylbenzyl chloride (10g, 49mmol) in DMF (100mL) was added HMPA (9.35mL, 54mmol) and KCN (3.5g, 54mmol). The resulting reaction mixture was stirred 18h at 80°C, then diluted with water and ethyl acetate. The organic extracts were washed (NaHCO₃, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 1:1 to 25:75) provided the (4-methanesulfonyl-phenyl)-acetonitrile compound.

Step 2:

10 3-[3-(6-Isopropylquinolin-8-yl)-phenyl]-2-[4-(methylsulfonyl)-phenyl]-prop-2-enenitrile

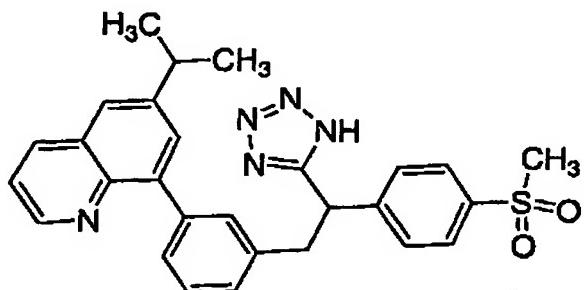
A solution of Quinoline **04** (5g, 18mmol), 4-methanesulfonylacetonitrile (3.5g, 18mmol) from Step 1 and piperidine (0.1mL) in toluene (5mL) was heated at 130°C. After 6h, the mixture was cooled to 21°C and 15 purified by flash chromatography (eluting with ethylacetate/hexane, 1:1 to 75:25) to afforded the title compound.

Step 3: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionitrile

20 A solution of the nitrile from Step 2 (400mg, 0.88mmol) in THF/EtOH (1:1, 10mL) containing Pd/C (10%, 40mg) was stirred under H₂ (1 atm) for 3 days. Filtration on celite, evaporation, stirring vigorously in ether for 1h then filtration afforded the 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionitrile compound as a white powder.

25 ¹H NMR (500MHz, acetone-*d*₆): δ 8.81 (dd, 1H), 8.31 (dd, 1H), 7.97 (d, 2H), 7.78 (s, 1H), 7.76 (d, 2H), 7.68 (s, 1H), 7.64 (d, 2H), 7.46 (q, 1H), 7.40 (t, 1H), 7.29 (d, 1H), 4.68 (t, 1H), 3.42 (dd, 2H), 3.15 (m, 1H), 3.08 (s, 3H), 1.38 (s, 6H).

6-Isopropyl-8-(3-[2-(4-methanesulfonyl-phenyl)-2-(1H-tetrazol-5-yl)-ethyl]-phenyl)-quinoline



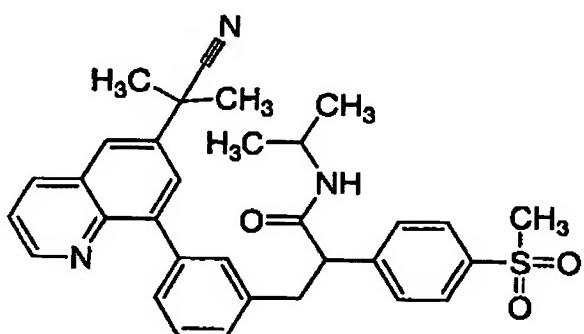
A solution of Example 78 (160mg, 0.35mmol), tri-n-butyltin chloride
 5 (0.478mL, 1.76mmol) and sodium azide (115mg, 1.76mmol) in xylene (5mL) was
 heated at 150°C for 18h. Cooling to 21°C, then purification by flash chromatography
 (eluting with CH₂Cl₂/MeOH, NH₄OH, 50:5:1) followed by stirring vigorously in ether
 for 1h, then filtered, afforded the title compound as a white powder.

¹H NMR (500MHz, acetone-d₆): δ 8.88 (d, 1H), 8.42 (d, 1H), 7.91 (d,
 10 2H), 7.83(s, 1H), 7.81 (d, 2H), 7.64 (dd, 2H), 7.56 (q, 1H), 7.49 (d, 1H), 7.29 (t, 1H),
 7.12 (d, 1H), 5.13 (q, 1H), 3.68 (q, 1H), 3.54 (q, 1H), 3.21 (m, 1H), 3.06 (s, 3H), 1.38
 (d, 6H).

15

EXAMPLE 80

3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-propionamide



Step 1: (E)-3-(3-Bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid

To a solution of 3-bromobenzaldehyde (12.9g, 70mmol) in toluene (100mL) was added 4-(methylsulfonyl)phenylacetic acid (15g, 70mmol) and piperidine (2mL). After overnight refluxing, the mixture was cooled down to r.t. To 5 the slurry thus formed, toluene was added (10mL). Filtration gave the (E)-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid as a white solid.

Step 2: (E)-N-Isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide

10 To a solution of (E)-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenoic acid from Step 1 (24.9g, 65mmol) in toluene (250mL) was added thionyl chloride (14.3mL, 196mmol) and triethylamine (34mL, 245mmol). After stirring at 21°C for 0.5h., isopropyl amine (28mL, 327mmol) was added. After a further 2h at r.t., the mixture was cooled to 0°C and was neutralised with saturated NH₄Cl solution, 15 then extracted with EtOAc. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (Hex:EtOAc, 1:1 to pure EtOAc) yielded the (E)-N-isopropyl-3-(3-bromophenyl)-2-[4-(methylsulfonyl)phenyl]-2-propenamide compound.

20 **Step 3: 3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-acrylamide**

Following the procedures described above in Example 62, Step 2, but substituting **Quinoline 08** for 8-bromoquinoline and purification by flash chromatography (eluting with ethylacetate/hexane, 75:25) afforded the 3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-acrylamide compound.

Step 4: 3-{3-[6-(Cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-

30 **methanesulfonyl-phenyl)-propionamide**

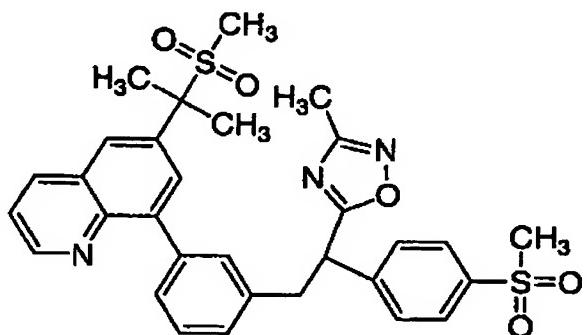
A solution of 3-{3-[6-(cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-acrylamide from **Step 3** (20mg, 0.038mmol) in THF (1mL) containing Pd/C (10%, 9mg) was stirred under H₂ (50 psi) for 18h. Filtration on celite, evaporation, and purification on HPLC (u-porasil ethyl acetate/hexane, 70:30 to 100:0, over 30min.) afforded the 3-{3-[6-(cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-propionamide compound as a foam.

- Example 80** can also be prepared according to the procedure described
- 10 in **Example 1** but using **Quinoline 09** and **Ester 05** as the starting material. After flash chromatography (hexane/EtOAc 50:50), the residue was stirred vigorously in ether for 1h then filtered to afford the 3-{3-[6-(cyano-dimethyl-methyl)-quinolin-8-yl]-phenyl}-N-isopropyl-2-(4-methanesulfonyl-phenyl)-propionamide compound as a white powder.
- 15 ¹H NMR (500MHz, acetone-*d*₆): δ 8.92 (dd, 1H), 8.46 (d, 1H), 8.11 (d, 1H), 7.86 (d, 3H), 7.72 (d, 2H), 7.65 (s, 1H), 7.58 (q, 1H), 7.51 (d, 1H), 7.35 (t, 1H), 7.28 (d, 1H), 7.12 (d, 1H), 3.96 (t, 1H), 3.85 (m, 1H), 3.51 (t, 1H), 3.07 (m, 4H), 1.85 (s, 6H), 0.93 (d, 3H), 0.88 (d, 3H).

20

EXAMPLE 81

6-(1-Methanesulfonyl-1-methyl-ethyl)-8-{3-[2-(4-methanesulfonyl-phenyl)-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl}-quinoline



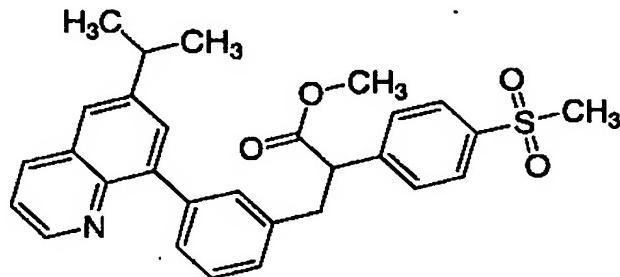
Example 81 was prepared according to the procedure described above in **Example 1** but using **Quinoline 01** and **Ester 06** as the starting material and the reaction performed from -78°C to 21°C. Flash chromatography (hexane/EtOAc 50:50 to 10:90) afforded the title compound.

5 ¹H NMR (500MHz, acetone-d₆): δ 8.91 (dd, 1H), 8.43 (dd, 1H), 8.24 (d, 1H), 8.01 (d, 1H), 7.90 (d, 2H), 7.74 (d, 2H), 7.60 (s, 1H), 7.54 (m, 2H), 7.33 (t, 1H), 7.25 (d, 1H), 4.97 (t, 1H), 3.73 (q, 1H), 3.48 (q, 1H), 3.06 (s, 3H), 2.70 (s, 3H), 2.31 (s, 3H), 1.96 (d, 6H).

10

EXAMPLE 82

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester



15 **Step 1:** 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester

Following the procedures described in **Example 13, Step 1**, but substituting **Quinoline 06** for **Quinoline 01**, the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester compound was obtained as a white foam.

20 **Step 2:** 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester

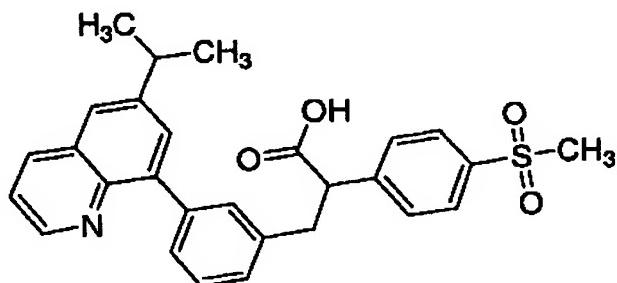
A solution of 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-(4-methylsulfanyl-phenyl)-propionic acid methyl ester from **Step 1** (1.05g, 2.3mmol),

NMO (655mg, 4.85mmol) and OsO₄ (4%, H₂O, 1mL, 0.16mmol) in THF (20mL) was stirred 18h at 21°C. The resulting reaction mixture was diluted with a sodium metabisulfite solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20) provided the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid methyl ester compound.

5 ¹H NMR (400MHz, acetone-d6): δ 8.81 (dd, 1H), 8.29 (dd, 1H), 7.89 (dd, 2H), 7.76 (d, 1H), 7.67 (d, 2H), 7.63 (d, 1H), 7.56-7.53 (m, 2H), 7.46 (dd, 1H),
10 7.32 (t, 1H), 7.21 (d, 1H), 4.23 (t, 1H), 3.61 (s, 3H), 3.54 (dd, 1H), 3.19-3.13 (m, 2H), 3.06 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H). LRMS (CI) 488 (M+H)⁺.

EXAMPLE 83

15 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(4-methanesulfonyl-phenyl)-propionic acid

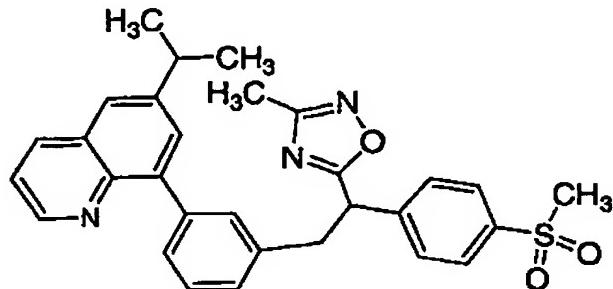


Following the procedures described in Example 8, but substituting Example 82 for Example 7, the title compound was obtained as a white solid.

20 ¹H NMR (400MHz, acetone-d6): δ 8.81 (dd, 1H), 8.29 (dd, 1H), 7.98 (d, 2H), 7.76 (s, 1H), 7.70 (d, 2H), 7.64 (dd, 1H), 7.59 (s, 1H), 7.54 (d, 1H), 7.47 (dd, 1H), 7.32 (t, 1H), 7.24 (d, 1H), 4.22 (t, 1H), 3.53 (dd, 1H), 3.20-3.13 (m, 2H), 3.07 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H). LRMS (CI) 474 (M+H)⁺ 430 (M+H - COOH)⁺.

EXAMPLE 84

6-Isopropyl-8-{3-[2-(4-methanesulfonyl-phenyl)-2-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl}-quinoline



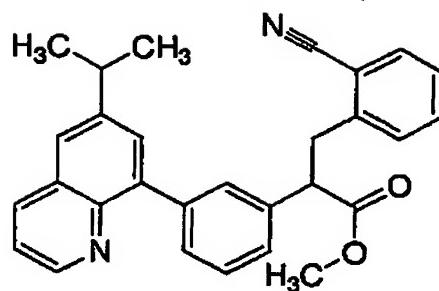
5 To a solution of Example 83 (177mg, 0.37mmol) in diglyme (3mL)
was added EDCI (93mg, 0.48mmol) and, after 10 min, N-hydroxyacetamidine (41mg,
0.55mmol). The resulting reaction mixture was stirred 3h at 110°C, then diluted with
a saturated sodium bicarbonate solution and ethyl acetate. The organic extracts were
washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash
10 chromatography (eluting with hexane/ethyl acetate, 80:20 to 100:0) provided the title
compound.

¹H NMR (400MHz, acetone-*d*6): δ 8.81 (dd, 1H), 8.30 (dd, 1H), 7.91 (dd, 2H), 7.77-7.74 (m, 3H), 7.59 (d, 1H), 7.56-7.53 (m, 2H), 7.47 (dd, 1H), 7.31 (t, 1H), 7.22 (d, 1H), 4.97 (t, 1H), 4.74 (dd, 1H), 3.48 (dd, 1H), 3.16 (q, 1H), 3.06 (s, 15 3H), 2.32 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H). LRMS (CI) 512 (M+H)⁺.

EXAMPLE 85

3-(2-Cyano-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester

20 ester



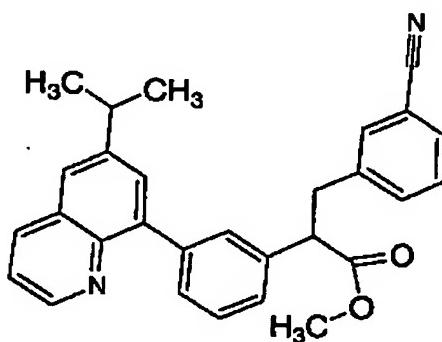
To a solution of **Quinoline 05** (100mg, 0.31mmol) in THF/DMF (1:1, 3mL) at -78°C was added potassium tert-butoxide (1M, 0.31mL, 0.31mmol) dropwise. The resulting reaction mixture was stirred 5min., then cannulated into a 5 solution of 2-cyanobenzylbromide (123mg, 0.63mmol) in THF (1mL) at 21°C. After 3h, the reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20 to 20:80) provided the title compound.

10 ¹H NMR (300MHz, acetone-d6): δ 8.81 (dd, 1H), 8.28 (dd, 1H), 7.50 (s, 1H), 4.19 (t, 1H), 3.65 (dd, 1H), 3.61 (s, 3H), 3.39 (dd, 1H), 3.15 (m, 1H), 1.37 (d, 6H).

15

EXAMPLE 86

3-(3-Cyano-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester

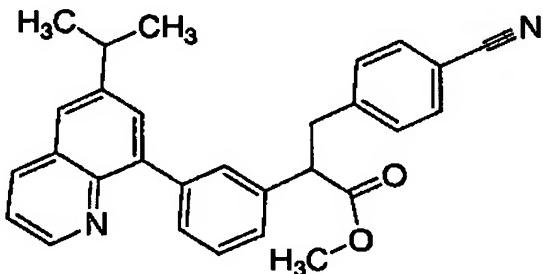


Following the procedures described above in Example 85, but substituting 3-cyanobenzylbromide for 2-cyanobenzylbromide, the title compound was obtained.

5 ^1H NMR (300MHz, acetone-*d*6): δ 8.83 (dd, 1H), 8.29 (dd, 1H), 7.76 (d, 1H), 7.68 (s, 2H), 7.65-7.30(m, 8H), 4.10 (t, 1H), 3.60 (s, 3H), 3.49 (dd, 1H), 3.20 (dd, 1H), 3.15 (m, 1H), 1.39 (d, 6H).

EXAMPLE 87

10 3-(4-Cyano-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester



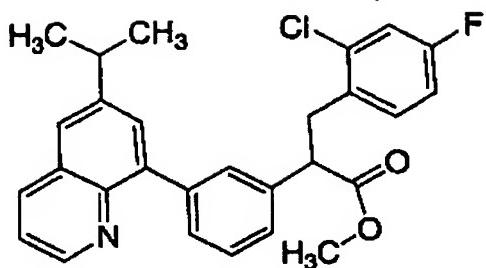
Following the procedures described above in Example 85, but substituting 4-cyanobenzylbromide for 2-cyanobenzylbromide, the title compound
15 was obtained.

1 ^1H NMR (300MHz, acetone-*d*6): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 7.80 (d, 1H), 7.70-7.30(m, 10H), 4.10 (t, 1H), 3.61 (s, 3H), 3.52 (dd, 1H), 3.25 (dd, 1H), 3.18 (m, 1H), 1.38 (d, 6H).

20

EXAMPLE 88

3-(2-Chloro-4-fluoro-phenyl)-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-propionic acid methyl ester



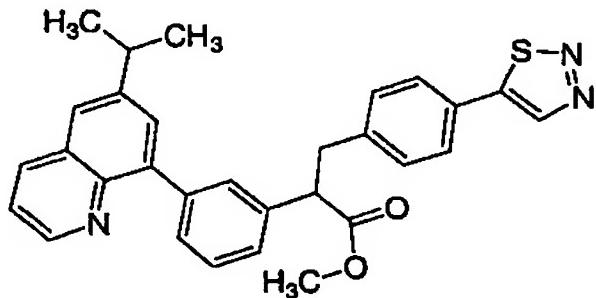
Following the procedures described above in Example 85, but substituting 2-chloro-4-fluorobenzyl bromide for 2-cyanobenzylbromide, the title compound was obtained.

5 ¹H NMR (300MHz, acetone-d6): δ 8.83 (dd, 1H), 8.28 (dd, 1H), 7.77-7.30 (m, 9H), 6.98 (dt, 1H), 4.13 (t, 1H), 3.61 (s, 3H), 3.53 (dd, 1H), 3.25 (dd, 1H), 3.17 (m, 1H), 1.38 (d, 6H).

10

EXAMPLE 89

2-[3-(6-isopropylquinolin-8-yl)-phenyl]-3-[4-(1,2,3-thiadiazol-5-yl)-phenyl]-propionic acid methyl ester



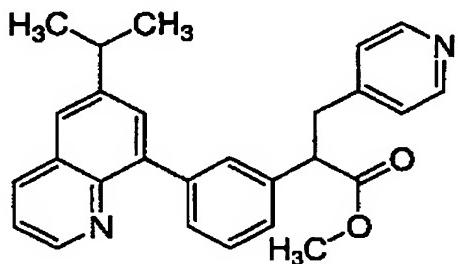
15 Following the procedures described above in Example 85, but substituting 4-(4-bromomethylphenyl)-[1,2,3]thiadiazole for 2-cyanobenzylbromide, the title compound was obtained.

1H NMR (400MHz, acetone-d6): δ 9.29 (s, 1H), 8.82 (dd, 1H), 8.30 (dd, 1H), 8.06 (d, 2H), 7.76 (d, 1H), 7.65-7.59 (m, 3H), 7.49-7.23 (m, 5H), 4.11 (t, 1H), 3.61 (s, 3H), 3.52 (dd, 1H), 3.22 (dd, 1H), 3.09 (m, 1H), 1.31 (d, 6H).

20

EXAMPLE 90

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-pyridin-4-yl-propionic acid methyl ester

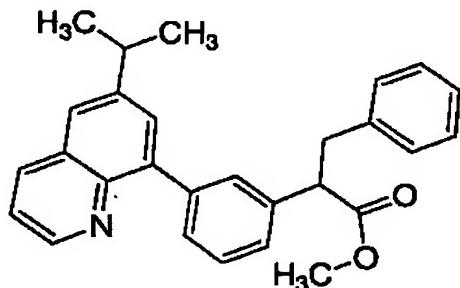


5 Following the procedures described above in Example 85, but substituting 4-picoly l chloride for 2-cyanobenzylbromide, the title compound was obtained.

10 ¹H NMR (300MHz, acetone-d₆): δ 8.82 (dd, 1H), 8.45 (d, 2H), 8.30 (dd, 1H), 7.80 (d, 1H), 7.70-7.35 (m, 6H), 7.25 (d, 2H), 4.15 (t, 1H), 3.60 (s, 3H), 3.46 (dd, 1H), 3.18 (m, 2H), 1.39 (d, 6H).

EXAMPLE 91

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-phenyl-propionic acid methyl ester



15

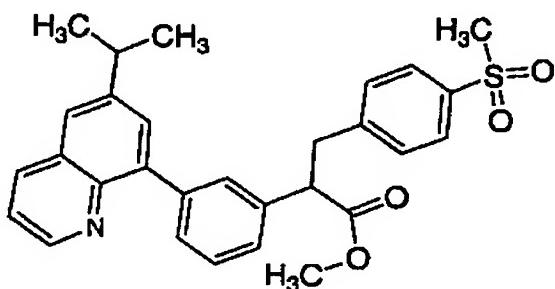
Following the procedures described above in Example 85, but substituting benzyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

¹H NMR (300MHz, acetone-d6): δ 8.81 (dd, 1H), 8.30 (dd, 1H), 7.77 (d, 1H), 7.70-7.10 (m, 11H), 4.05 (t, 1H), 3.60 (s, 3H), 3.45 (dd, 1H), 3.18 (m, 1H), 3.12 (dd, 1H), 1.40 (d, 6H).

5

EXAMPLE 92

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionic acid methyl ester

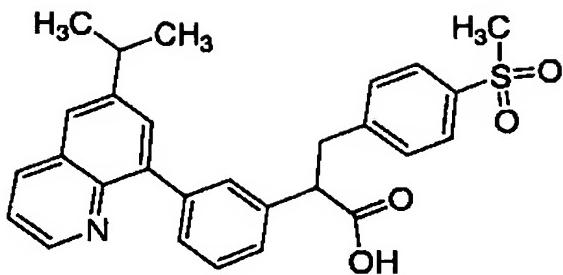


10 Following the procedures described above in Example 85, but substituting 4-methanesulfonylbenzyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

15 ¹H NMR (400MHz, acetone-d6): δ 8.85 (dd, 1H), 8.32 (dd, 1H), 7.81 (m, 3H), 7.72 (s, 1H), 7.69 (s, 1H), 7.61 (d, 1H), 7.56 (d, 2H), 7.49 (dd, 1H), 7.40 (t, 1H), 7.34 (d, 1H), 4.12 (t, 1H), 3.60 (s, 3H), 3.55 (dd, 1H), 3.38 (dd, 1H), 3.29 (m, 1H), 3.05 (s, 3H), 1.38 (d, 6H).

EXAMPLE 93

20 2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionic acid

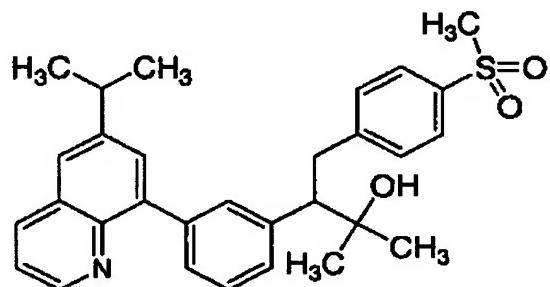


Following the procedures described above in **Example 8**, but substituting **Example 92** for **Example 7**, the title compound was obtained.

- ¹H NMR (400MHz, acetone-*d*6): δ 8.85 (dd, 1H), 8.31 (dd, 1H), 7.82 (d, 2H), 7.78 (d, 2H), 7.68 (s, 1H), 7.60 (m, 3H), 7.48 (dd, 1H), 7.40 (m, 2H), 4.10 (t, 1H), 3.55 (dd, 1H), 3.25 (dd, 1H), 3.18 (m, 1H), 3.05 (s, 3H), 1.38 (s, 6H).

EXAMPLE 94

- 10 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-4-(4-methanesulfonyl-phenyl)-2-methylbutan-2-ol



- To a solution of **Example 92** (100mg, 0.2mmol) in CH₂Cl₂ (2mL) at -78°C was added methylmagnesium chloride (3M, THF, 0.2mL, 0.6mmol) dropwise.
- 15 The resulting reaction mixture was stirred 1h at 21°C, then quenched with a saturated ammonium chloride solution. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 7:3) provided the title compound.

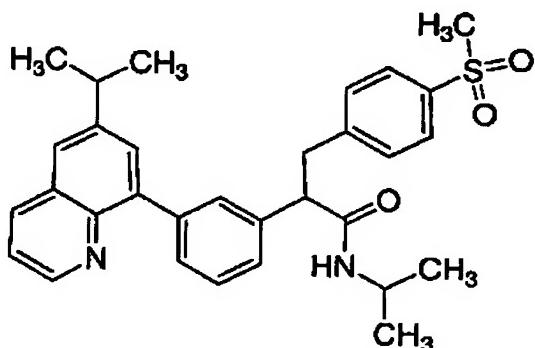
- ¹H NMR (300MHz, acetone-*d*6): δ 8.85 (dd, 1H), 8.30 (dd, 1H), 7.80-20 (m, 5H), 7.55-7.45 (m, 4H), 7.35-7.20 (m, 2H), 3.70 (brs, 1H), 3.60 (dd, 1H),

3.30 (t, 1H), 3.15 (dd, 1H), 3.12 (m, 1H), 3.00 (s, 3H), 1.38 (d, 6H), 1.30 (s, 3H), 1.25 (s, 3H).

5

Example 95

N-Isopropyl-2-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionamide



To a solution of Example 93 (100mg, 0.21mmol) in CH₂Cl₂ (2mL)

10 was added DMAP (26mg, 0.21mmol), EDCI (45mg, 0.23mmol), then isopropyl amine (1mL, 12mmol). The resulting reaction mixture was stirred 18h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20 to 20:80) provided the

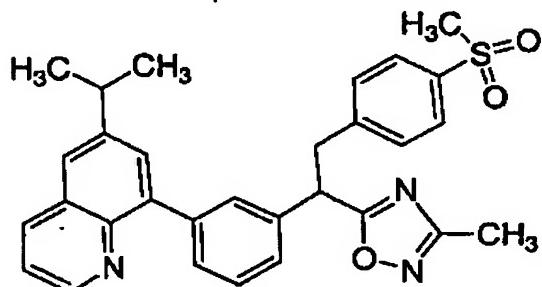
15 title compound.

¹H NMR (300MHz, acetone-*d*6): δ 8.82 (dd, 1H), 8.35 (dd, 1H), 7.95 (m, 1H), 7.85-7.75 (m, 4H), 7.65-7.52 (m, 3H), 7.50 (dd, 1H), 7.45-7.35 (m, 2H), 7.10 (brd, 1H), 3.88 (m, 2H), 3.59 (dd, 1H), 3.15 (m, 2H), 3.09 (s, 3H), 1.38 (d, 6H), 0.99 (d, 3H), 0.96 (d, 3H).

20

EXAMPLE 96

6-Isopropyl-8-{3-[2-(4-methanesulfonyl-phenyl)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-phenyl}-quinoline



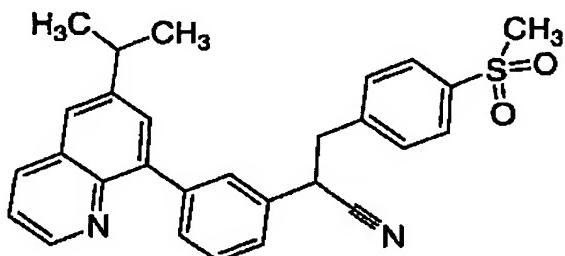
Following the procedures described above in **Example 84**, but
5 substituting **Example 93** for **Example 83**, the title compound was obtained.

¹H NMR (300MHz, acetone-*d*6): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 7.80 (m, 4H), 7.70-7.58 (m, 4H), 7.50 (dd, 1H), 7.40 (m, 2H), 4.85 (t, 1H), 3.78 (dd, 1H), 3.60 (dd, 1H), 3.28 (m, 1H), 3.05 (s, 3H), 2.30 (s, 3H), 1.40 (d, 6H).

10

EXAMPLE 97

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-propionitrile

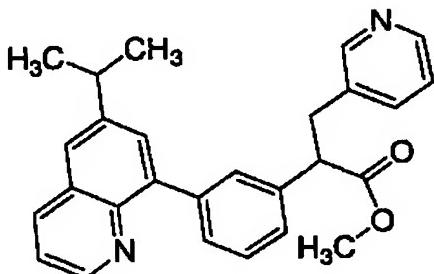


Following the procedures described above in **Example 85**, but
15 substituting **Quinoline 07** for **Quinoline 05** and substituting 4-methanesulfonylbenzyl chloride for 2-cyanobenzylbromide, the title compound was obtained.

¹H NMR (300MHz, acetone-*d*6): δ 8.85 (dd, 1H), 8.30 (dd, 1H), 7.90 (d, 2H), 7.80 (m, 2H), 7.70 (m, 2H), 7.60 (d, 2H), 7.45 (m, 3H), 4.57 (t, 1H), 3.45 (d, 2H), 3.19 (m, 1H), 3.09 (s, 3H), 1.40 (d, 6H).

EXAMPLE 98

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-pyridin-3-yl-propionic acid methyl ester



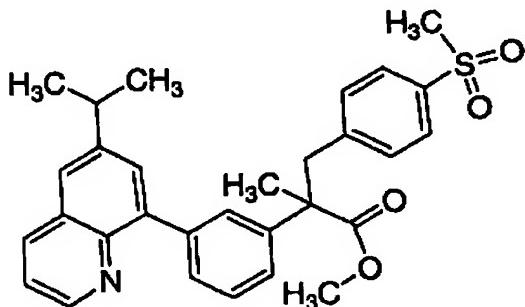
Following the procedures described above in Example 85, but substituting 3-picoly l chloride for 2-cyanobenzylbromide, the title compound was obtained.

10 ^1H NMR (400MHz, acetone-*d*6): δ 8.82 (dd, 1H), 8.48 (d, 1H), 8.38 (dd, 1H), 8.29 (dd, 1H), 7.77 (d, 1H), 7.68 (t, 1H), 7.64 (m, 3H), 7.47 (dd, 1H), 7.41 (t, 1H), 7.34 (d, 1H), 7.22 (dd, 1H), 4.06 (t, 1H), 3.59 (s, 3H), 3.42 (dd, 1H), 3.16 (m, 2H), 1.37 (d, 6H).

15

EXAMPLE 99

2-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-3-(4-methanesulfonyl-phenyl)-2-methyl-propionic acid methyl ester

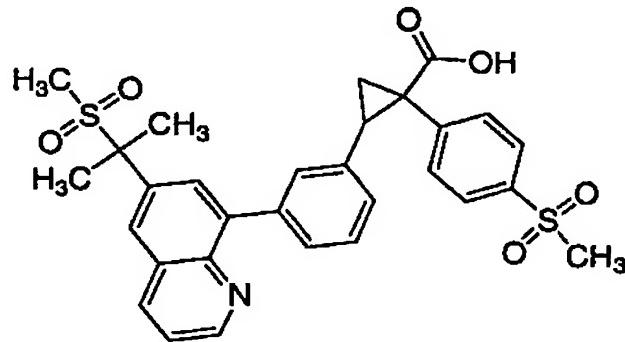


To a solution of **Example 92** (90mg, 0.185mmol) in THF/DMF (1:1, 2mL) at -78°C was added potassium tert-butoxide (1M, 0.19mL, 0.19mmol) dropwise followed by MeI (0.014mL, 0.22mmol) after 15 min. The resulting reaction mixture was stirred 18h at 21°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 50:50) provided the title compound.

¹H NMR (300MHz, acetone-d6): δ 8.84 (dd, 1H), 8.30 (dd, 1H), 7.80-7.70 (m, 5H), 7.62 (d, 1H), 7.49 (dd, 1H), 7.40 (m, 3H), 7.30 (d, 1H), 3.70 (s, 3H), 3.52 (dd, 2H), 3.20 (m, 1H), 3.03 (s, 3H), 1.55 (s, 3H), 1.40 (d, 6H).

EXAMPLE 100

¹⁵ 2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)cyclopropanecarboxylic acid



Step 1: 3-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-acrylic acid

²⁰ Following the procedures described above in **Example 80, Step 1**, but substituting **Quinoline 03** for 3-bromobenzaldehyde, the 3-{3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-2-(4-methanesulfonyl-phenyl)-acrylic acid compound was obtained as a white solid.

Step 2: 3-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-2-(4-methanesulfonyl-phenyl)-acrylic acid methyl ester

Following the procedures described above in **Ester 01**, the 3-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-2-(4-methanesulfonyl-phenyl)-acrylic acid methyl ester compound was obtained as a white solid.

Step 3: 2-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid methyl ester

To a suspension of trimethylsulfoxonium iodide (400mg, 1.83mmol) in DMSO (25mL) at 0°C was added NaH (60%, 73mg, 1.83mmol). After 30min., 3-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-2-(4-methanesulfonyl-phenyl)-acrylic acid methyl ester from **Step 2** (688mg, 1.22mmol) was added and the resulting reaction mixture stirred for 18h at 21°C, then diluted with water and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with toluene/acetone, 80:20) provided the 2-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid methyl ester compound.

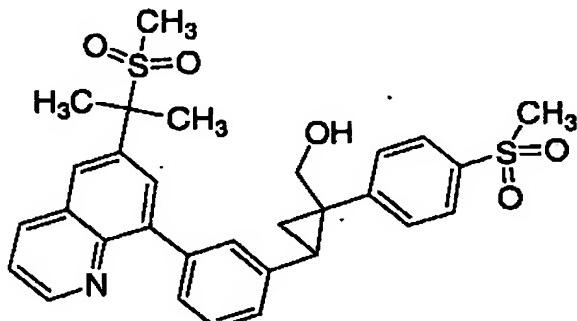
Step 4: 2-[3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid

Following the procedures described above in **Example 08**, the 2-[3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl]-1-(4-methanesulfonyl-phenyl)-cyclopropanecarboxylic acid compound was obtained as a white solid.

¹H NMR (400MHz, acetone-d6): δ 8.91 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.13 (d, 1H), 7.92 (d, 2H), 7.85 (d, 2H), 7.80 (s, 1H), 7.66 (d, 1H), 7.55 (dd, 1H), 7.52 (d, 1H), 7.45 (m, 1H), 3.12 (s, 3H), 3.06 (t, 1H), 2.73 (s, 3H), 2.42 (dd, 1H), 1.98 (s, 6H), 1.74 (dd, 1H).

EXAMPLE 101

[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropyl]-methanol



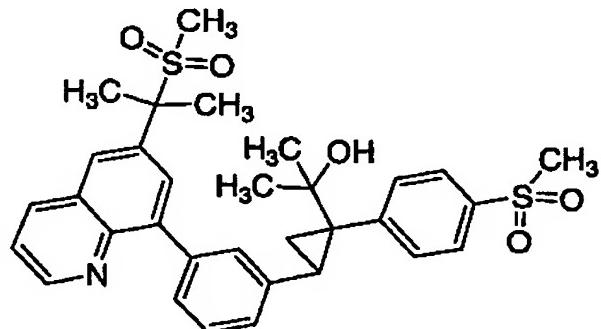
5 Using the compound from Example 100, Step 3 as the starting material and following the procedures described above in Example 15 and purification by flash chromatography (eluting with CH₂Cl₂/ethyl acetate, 60:40) provided the title compound.

10 ¹H NMR (300MHz, acetone-*d*6) : δ 8.86 (dd, 1H), 8.45 (dd, 1H), 8.28 (d, 1H), 8.20 (d, 1H), 7.91 (brs, 1H), 7.87 (d, 2H), 7.80 (d, 2H), 7.55 (m, 2H), 7.48 (m, 2H), 3.95 (dd, 1H), 3.75 (dd, 1H), 3.55 (dd, 1H), 3.09 (s, 3H), 2.75 (m, 1H), 2.71 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.58 (dd, 1H), 1.46 (dd, 1H).

15

EXAMPLE 102

2-[2-{3-[6-(1-Methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl}-1-(4-methanesulfonyl-phenyl)-cyclopropyl]-propan-2-ol



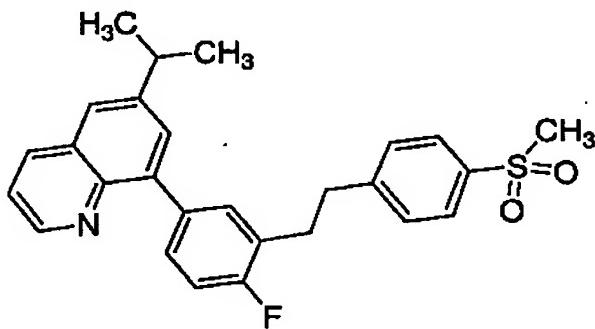
Using the compound from Example 100, Step 3 as the starting material and following the procedures described above in Example 29 and purification by flash chromatography (eluting with CH₂Cl₂/ethyl acetate, 60:40) provided the title compound.

5 ¹H NMR (300MHz, acetone-d6): δ 8.90 (dd, 1H), 8.45 (dd, 1H), 8.28 (d, 1H), 8.19 (d, 1H), 7.99 (s, 1H), 7.87 (s, 4H), 7.56 (m, 3H), 7.47 (t, 1H), 3.10 (s, 3H), 2.72 (s, 3H), 2.55 (t, 1H), 2.04 (m, 1H), 2.00 (s, 3H), 1.99 (s, 3H), 1.32 (dd, 1H), 1.17 (s, 3H), 1.06 (s, 3H).

10

EXAMPLE 103

8-{4-Fluoro-3-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline



Step 1: 4-Fluoro-3-hydroxymethyl-benzene-boronic acid

15 To a solution of 4-bromo-2-fluoro-benzyl alcohol (10g, 49mmol) in THF (500mL) at -78°C was added BuLi (2.5M, 43mL, 107mmol) dropwise keeping the internal temperature below -73°C. After 25 min., trimethylborate (25mL, 107mmol) was added and the resulting reaction mixture stirred for 15h at -78°C, 1h at 21°C, then diluted with HCl 10% and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. The residue was solidified from hexane/ethyl acetate with water (5 drops) to afford the 4-fluoro-3-hydroxymethyl-benzene-boronic acid compound as a white solid.

20

Step 2: [2-Fluoro-5-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol

Following the procedures described above in **Quinoline 01, Step 3**, and purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the [2-fluoro-5-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol compound.

5 **Step 3: 2-Fluoro-5-(6-isopropyl-quinolin-8-yl)-benzaldehyde**

A solution of [2-fluoro-5-(6-isopropyl-quinolin-8-yl)-phenyl]-methanol from **Step 2** (2.23g, 7.55mmol) and MnO₂ (13g, 150mmol) in CH₂Cl₂ (70mL) was stirred at 21°C for 18h. The mixture was filtered through a pad of celite and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the 2-fluoro-5-(6-isopropyl-quinolin-8-yl)-benzaldehyde compound.

Step 4: 8-{4-Fluoro-3-[2-(4-methanesulfonyl-phenyl)-vinyl]-phenyl}-6-isopropyl-quinoline

15 A solution of 4-methanesulfonylbenzyl chloride (10g, 49mmol) and triphenylphosphine (12.8g, 49mmol) in acetonitrile (100mL) was stirred for 18h at reflux. The resulting reaction mixture was cooled to 21°C and the phosphorus salt crystallised from CH₃CN/ether. To a suspension of the salt (875mg, 1.87mmol) in THF (15mL) at 0°C was added potassium tert-butoxide (1M, THF, 1.87mL, 1.87mmol) dropwise and the resulting mixture stirred 30min at 0°C. The mixture was cooled to -78°C and the 2-fluoro-5-(6-isopropyl-quinolin-8-yl)-benzaldehyde from **Step 3** (0.5g, 1.7mmol, in THF) was added. After 90min. at 21°C, the reaction mixture was diluted with HCl 10% and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 60:40) provided the 8-{4-fluoro-3-[2-(4-methanesulfonyl-phenyl)-vinyl]-phenyl}-6-isopropyl-quinoline compound as a mixture of isomer (3:1).

Step 5: 8-{4-Fluoro-3-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline

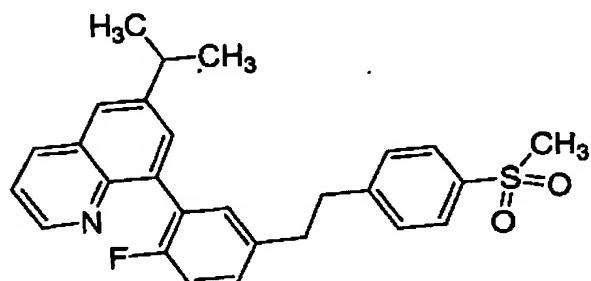
A solution of 8-{4-fluoro-3-[2-(4-methanesulfonyl-phenyl)-vinyl]-phenyl}-6-isopropyl-quinoline from Step 4 (200mg, 0.45mmol) and polymer supported phenylsulfonyl hydrazide (1.0g) in toluene (10mL) was heated at 100°C for 18h. The resulting mixture was cooled at 21°C, filtered and the solvent evaporated.

5 Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30 to 40:60) provided the 8-{4-fluoro-3-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline compound.

10 ^1H NMR (300MHz, acetone-*d*6): δ 8.82 (dd, 1H), 8.30 (dd, 1H), 7.87 (d, 2H), 7.78 (dd, 1H), 7.70-7.59 (m, 3H), 7.55 (d, 2H), 7.45 (dd, 1H), 7.17 (dd, 1H), 3.15 (m, 1H), 3.10 (brs, 4H), 3.05 (s, 3H), 1.40 (d, 6H).

EXAMPLE 104

8-{2-Fluoro-5-[2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl}-6-isopropyl-quinoline.



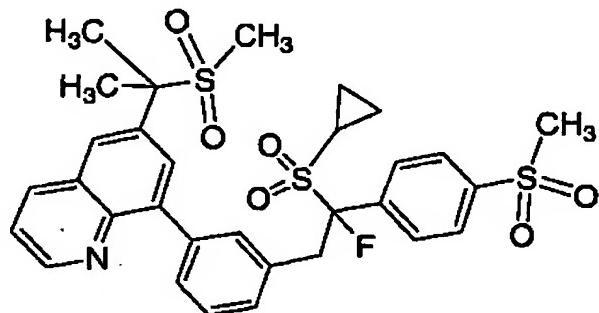
15

Following the procedures described above in Example 103, but substituting 3-bromo-4-fluorobenzyl alcohol for 4-bromo-2-fluoro-benzyl alcohol, the title compound was obtained.

16 ^1H NMR (300MHz, acetone-*d*6): δ 8.78 (dd, 1H), 8.30 (dd, 1H), 7.83 (d, 2H), 7.81 (d, 1H), 7.63 (d, 1H), 7.51 (d, 2H), 7.45 (dd, 1H), 7.32 (m, 2H), 7.10 (dd, 1H), 3.15 (m, 1H), 3.10 (m, 4H), 3.04 (s, 3H), 1.37 (d, 6H).

EXAMPLE 105

8-[3-[2-Cyclopropanesulfonyl-2-fluoro-2-(4-methanesulfonyl-phenyl)-ethyl]-phenyl]-6-(1-methanesulfonyl-1-methyl-ethyl)-quinoline



Following the procedures described above in **Example 1**, but

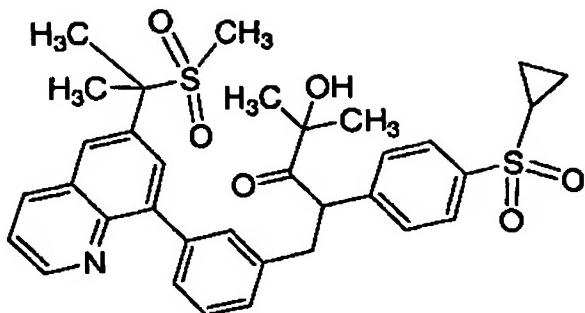
- 5 substituting **Sulfone 03** for **Ketone 02** and then using the procedures described in **Example 37** (2 steps in a one pot reaction) followed by purification by flash chromatography (eluting with ethyl acetate/hexane) afforded the title compound as a pale beige powder. The enantiomers can be separated on a chiral column (ChiralPaK AD, hexane/EtOH/i-PrOH/MeOH, 30:30:30:10, retention time 8.1 and 10.2 min) to
- 10 give **Examples 105A** and **Example 105B**.

¹H NMR (400MHz, ace-d6): δ 8.88 (dd, 1H), 8.42 (dd, 1H), 8.23 (d, 1H), 8.01-7.94 (m, 5H), 7.57-7.53 (s, 3H), 7.30 (t, 1H), 7.24 (d, 1H), 4.05-3.97 (m, 2H), 3.08 (s, 3H), 2.70 (s, 3H), 2.49-2.43 (m, 1H), 1.97 (s, 3H), 1.96 (s, 3H), 1.18-1.08 (m, 2H), 1.00-0.93 (m, 1H), 0.84-0.77 (m, 1H).

15

EXAMPLE 106

2-(4-Cyclopropanesulfonyl-phenyl)-4-hydroxy-1-(3-[6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl]-phenyl)-4-methyl-pentan-3-one

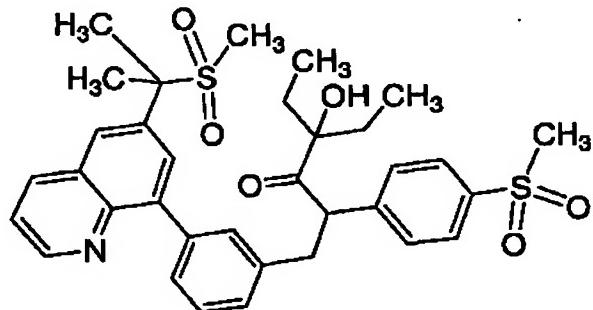


Example 106 was prepared by following the procedures described above in Example 1, but substituting Sulfone 09 for Ketone 02. Purification by flash chromatography (eluting with ethyl acetate/hexane, 1:1 to 8:2) afforded the title compound.

¹H NMR (400MHz, ace-d6): δ 8.93 (dd, 1H), 8.44 (dd, 1H), 8.26 (d, 1H), 8.05 (d, 1H), 7.83 (d, 2H), 7.67 (d, 2H), 7.58-7.54 (m, 2H), 7.51 (app d, 1H), 7.33 (t, 1H), 7.22 (app d, 1H), 5.18 (d, 1H), 4.48 (s, 1H), 3.45 (dd, 1H), 3.07 (dd, 1H), 2.71 (s, 3H), 2.60 (m, 1H), 1.95 (s, 6H), 1.14 (dd, 2H), 1.10 (s, 3H), 1.05 (s, 3H), 1.00 (m, 2H).

EXAMPLE 107

4-Ethyl-4-hydroxy-1-[3-{6-(1-methanesulfonyl-1-methyl-ethyl)-quinolin-8-yl}-phenyl]-2-(4-methanesulfonyl-phenyl)-hexan-3-one



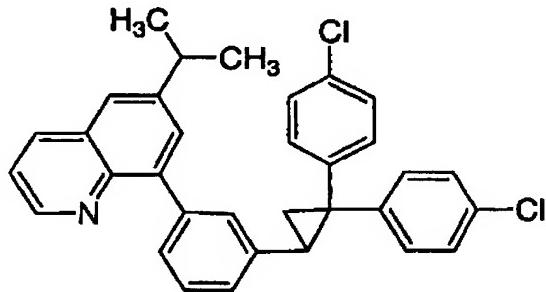
Example 107 was prepared by following the procedures described above in Example 1, but substituting Ketone 12 for Ketone 02. Purification by flash

chromatography (eluting with ethyl acetate/hexane, 3:2) afforded the title compound as a white foam.

¹H NMR (400MHz, acetone-d₆): δ 9.93 (dd, 1H), 8.44 (dd, 1H), 8.25 (d, 1H), 8.03 (d, 1H), 7.85 (m, 2H), 7.67 (m, 2H), 7.57 (m, 2H), 7.48 (dd, 1H), 7.32 (t, 1H), 7.20 (dd, 1H), 5.13 (t, 1H), 4.15 (s, OH), 3.42 (dd, 1H), 3.09 (dd, 1H), 3.03 (s, 3H), 2.72 (s, 3H), 1.98 (s, 6H), 1.6-1.4 (m, 4H), 0.49 (t, 6H).

EXAMPLE 108

10 8-{3-[2,2-Bis-(4-chloro-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline



Step 1: [Bis-(4-chloro-phenyl)-methylene]-hydrazine

A solution of bis-(4-chloro-phenyl)-methanone (5.0g, 19.9mmol) and hydrazine monohydrate (5mL, 103mmol) in ethanol (25mL) was heated to reflux 18h, cooled to 21°C, and filtered to afford the [bis-(4-chloro-phenyl)-methylene]-hydrazine compound as a yellow solid.

Step 2: Diazo bis-(4-chloro-phenyl)-methane

To a solution of [bis-(4-chloro-phenyl)-methylene]-hydrazine from Step 1 (2.0g, 7.5mmol) in CHCl₃ (20mL) was added MnO₂ (5.0g, 57mmol). The resulting reaction mixture was stirred 1h at 21°C, then filtered on a bed of MgSO₄ and the filtrate concentrated to provide the diazo bis-(4-chloro-phenyl)-methane compound as a purple solid.

25 **Step 3: 6-Isopropyl-8-(3-vinyl-phenyl)-quinoline**

To a solution of methyl triphenylphosphonium bromide (5.2g, 14.6mmol) in THF (20mL) at 0°C was added potassium tert-butoxide (1M, THF, 14.5mL, 14.5mmol) followed, after 15 min, by Quinoline 04 (3.33g, 12.1mmol) in THF (5mL). The resulting reaction mixture was stirred 2h at 0°C, then diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 90:10) provided the 6-isopropyl-8-(3-vinyl-phenyl)-quinoline compound.

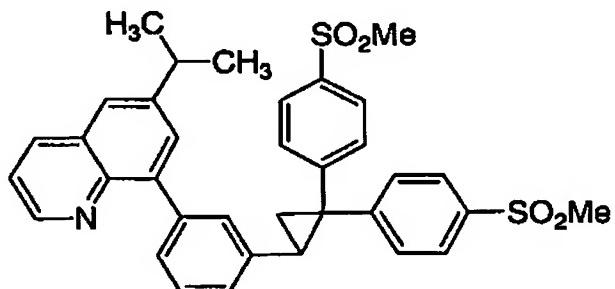
- 10 Step 4: 8-{3-[2,2-Bis-(4-chloro-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline
A solution of the 6-isopropyl-8-(3-vinyl-phenyl)-quinoline from Step 3 (230mg, 0.84mmol) and the diazo bis-(4-chloro-phenyl)-methane from Step 2 (530mg, 2.0mmol) in benzene (10mL) was heated to reflux for 18h, cooled to 21°C, and purified by flash chromatography (eluting with hexane/ethyl acetate, 90:10) to provide the 8-{3-[2,2-bis-(4-chloro-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline compound as a yellow foam.

15
¹H NMR (400MHz, acetone-d₆): δ 8.79 (dd, 1H), 8.28 (dd, 1H), 7.73 (d, 1H), 7.47-7.39 (m, 4H), 7.33-7.21 (m, 8H), 7.14 (m, 2H), 3.13 (m, 1H), 3.03 (dd, 1H), 2.18 (dd, 1H), 1.80 (dd, 1H), 1.36 (d, 6H).

20

EXAMPLE 109

8-{3-[2,2-Bis-(4-methanesulfonyl-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline



25

Step1: Bis-(4-methylsulfanyl-phenyl)-methanol

To a solution of 4-bromothioanisole (1.06g, 5.2mmol) in THF (20mL) at -78°C was added BuLi (2.3M, hexane, 2.2mL, 5mmol) dropwise. After 30min at -78°C, 4-methylthiobenzaldehyde (685mg, 4.5mmol) was added. After 20 min., the 5 resulting reaction mixture was diluted with a saturated ammonium chloride solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 80:20) provided the bis-(4-methylsulfanyl-phenyl)-methanol compound.

10

Step 2: Bis-(4-methylsulfanyl-phenyl)-methanone

A solution of bis-(4-methylsulfanyl-phenyl)-methanol from Step 1 (1.0g, 3.6mmol) and MnO₂ (3g, 35mmol) in CH₂Cl₂ (30mL) was stirred at 21°C for 18h. The resulting mixture was filtered through a pad of celite and concentrated. 15 Purification by flash chromatography (eluting with hexane/ethyl acetate, 85:15) provided the bis-(4-methylsulfanyl-phenyl)-methanone compound.

Step 3: Bis-(4-methanesulfonyl-phenyl)-methanone

A solution of bis-(4-methylsulfanyl-phenyl)-methanone from Step 2 (0.9g, 3.2mmol), NMO (2.2g, 19mmol) and OsO₄ (4%, H₂O, 1mL, 0.16mmol) in acetone (20mL) was stirred 18h at 21°C. The resulting reaction mixture was diluted with a sodium metabisulfite solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with hexane/ethyl acetate, 70:30) provided the bis-(4- 25 methanesulfonyl-phenyl)-methanone compound.

Step 4: 8-{3-[2,2-Bis-(4-methanesulfonyl-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline

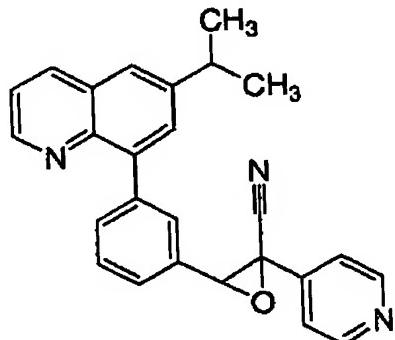
The procedures described above in Example 108 were followed, but 30 substituting bis-(4-methanesulfonyl-phenyl)-methanone from Step 3 instead of bis-(4-chloro-phenyl)-methanone. Purification by flash chromatography (eluting with ethyl

acetate/hexane, 3:7) afforded the 8-{3-[2,2-bis-(4-methanesulfonyl-phenyl)-cyclopropyl]-phenyl}-6-isopropyl-quinoline compound as a white solid.

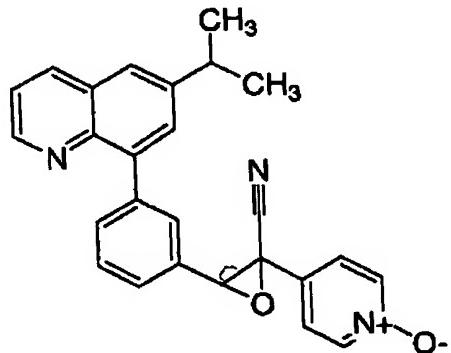
¹H NMR (400MHz, acetone-d₆): δ 8.81 (dd, 1H), 8.29 (dd, 1H), 7.88 (d, 2H), 7.76-7.70 (m, 5H), 7.58 (d, 2H), 7.48-7.40 (m, 4H), 7.21 (t, 1H), 7.05 (d, 1H), 5 3.23 (dd, 1H), 3.14 (m, 1H), 3.09 (s, 3H), 2.93 (s, 3H), 2.4 (dd, 1H), 1.97 (dd, 1H), 1.35 (d, 6H).

EXAMPLES 110 and 111

10 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-oxirane-2-carbonitrile
and
3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-4-yl)-oxirane-2-carbonitrile



15



Step 1: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-acrylonitrile

Following the procedures described above in Example 78, Step 2, but substituting 4-methanesulfonylacetonitrile for 4-pyridinylacetonitrile, and purification by flash chromatography (eluting with ethyl acetate/hexane, 3:7) afforded the 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-acrylonitrile compound.

Step 2: 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-oxirane-2-carbonitrile

To a solution of 3-[3-(6-isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-acrylonitrile from Step 1 (75mg, 0.3mmol) in CH₂Cl₂/MeOH (1:1, 2mL) was added MMPP (148mg, 0.3mmol). The resulting reaction mixture was stirred 18h at 21°C, then diluted with a sodium bicarbonate solution and ethyl acetate. The organic extracts were washed (H₂O, brine), dried (MgSO₄), filtered and concentrated. Purification by flash chromatography (eluting with EtOH/ethyl acetate, 10:90) provided the title compounds.

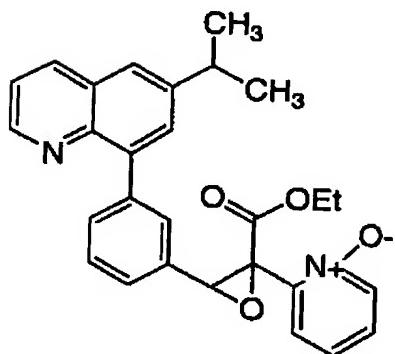
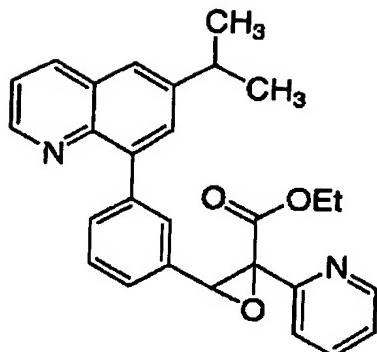
15 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-4-yl-oxirane-2-carbonitrile: ¹H NMR (500MHz, acetone-d₆): δ 8.83 (dd, 1H), 8.74 (m, 2H), 8.32 (dd, 1H), 7.95 (d, 1H), 7.90 (m, 1H), 7.81 (d, 1H), 7.79 (d, 1H), 7.61 (m, 2H), 7.56 (dd, 2H), 7.49 (dd, 1H), 4.7 (s, 1H), 3.18 (m, 1H), 1.38 (d, 3H), 1.37 (d, 3H).

20 3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-4-yl)-oxirane-2-carbonitrile: ¹H NMR (500MHz, acetone-d₆): δ 8.83 (dd, 1H), 8.33 (dd, 1H), 8.27 (m, 2H), 7.92 (s, 1H), 7.90 (m, 1H), 7.81 (d, 1H), 7.78 (d, 1H), 7.61-7.56 (m, 4H), 7.50 (dd, 1H), 4.8 (s, 1H), 3.18 (m, 1H), 1.39 (d, 3H), 1.37 (d, 3H).

25

EXAMPLES 112 and 113

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-2-yl-oxirane-2-carboxylic acid ethyl ester
and
3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-2-yl)-oxirane-2-carboxylic acid ethyl ester



Following the procedures described in Example 110, but substituting
 5 4-pyridinylacetonitrile for ethyl 2-pyridinylacetate, and purification by flash chromatography (eluting with EtOH/ethyl acetate, 10:90) provided the title compounds.

3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-pyridin-2-yl-oxirane-2-carboxylic acid ethyl ester: ^1H NMR (500MHz, acetone- d_6): δ 8.80 (dd, 1H), 8.29 (dd, 1H), 8.05 (d, 1H), 7.76 (d, 1H), 7.61 (m, 1H), 7.57 (s, 1H), 7.53 (dd, 1H), 7.50 (d, 1H), 7.46 (dd, 1H), 7.35-7.27 (m, 5H), 5.11 (s, 1H), 4.20 (m, 2H), 3.16 (m, 1H), 1.37 (d, 6H), 1.20 (t, 3H).

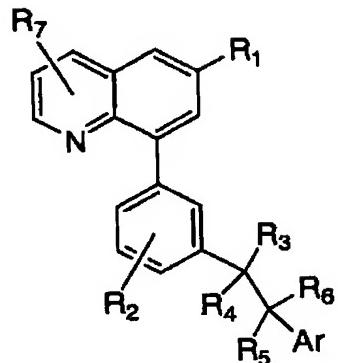
3-[3-(6-Isopropyl-quinolin-8-yl)-phenyl]-2-(1-oxy-pyridin-2-yl)-oxirane-2-carboxylic acid ethyl ester: ^1H NMR (500MHz, acetone- d_6): δ 8.83 (dd, 1H), 8.59 (d, 1H), 8.31 (dd, 1H), 7.89 (m, 1H), 7.87 (m, 2H), 7.75 (m, 2H), 7.48 (m,

3H), 7.42 (m, 1H), 4.9 (s, 1H), 4.05 (m, 2H), 3.18 (m, 1H), 1.39 (d, 3H), 1.37 (d, 3H), 0.89 (t, 3H).

Other variations or modifications, which will be obvious to those skilled in the art, are within the scope and teachings of this invention. This invention is not to be limited except as set forth in the following claims.

WHAT IS CLAIMED IS:

1. A compound represented by (I):



5

(I)

or a pharmaceutically acceptable salt thereof, wherein

Ar is phenyl, pyridinone, pyridyl, or pyridyl N-oxide, optionally substituted with 1-5 independent -C1-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C1-6alkyl), -(C0-6alkyl)-SO_n-NH-(C1-6alkyl) or 5-membered

10 heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C1-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃;

R₁ is hydrogen, halogen; or a -C1-6alkyl, -cycloC₃-6alkyl,

-C1-6alkenyl, -C₀-4alkyl-C(O)-C₀-4alkyl, -C1-6alkoxy, aryl, heteroaryl, -CN,

15 -heterocycloC₃-6alkyl, -amino, -C1-6alkylamino, -(C1-6alkyl)(C1-6alkyl)amino, -C₁-6alkyl(oxy)C1-6alkyl, -C(O)NH(aryl), -C(O)NH(heteroaryl), -SO_nNH(aryl), -SO_nNH(heteroaryl), -SO_nNH(C1-6alkyl), -C(O)N(C0-6alkyl)(C0-6alkyl), -NH-SO_n-(C1-6alkyl), -carbamoyl, -(C1-6alkyl)-O-C(CN)-dialkylamino, or -(C0-6alkyl)-SO_n-(C1-6alkyl) group, wherein any of the groups is optionally substituted

20 with 1-5 substituents; wherein each substituent is independently a halogen, -OH, -CN, -C₁-C₆alkyl, -C(O)(heterocycloC₃-6alkyl), -C(O)-O-(C₀-6alkyl), -C(O)-O-aryl, alkoxy, cycloalkyloxy, acyl, acyloxy, -cycloC₃-6alkyl, heterocycloC₃-6alkyl, aryl, heteroaryl, pyridyl N-oxide, carbonyl, carbamoyl, or -SO_n-(C1-6alkyl);

R₂, R₃, R₆, and R₇ are each independently hydrogen, halogen,

25 hydroxyl, -C1-6alkyl, or -C1-6alkoxy, wherein the alkyl and alkoxy are optionally substituted with 1-3 independently halogen or OH;

R₄ is hydrogen, halogen, -CN, phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl, wherein the phenyl, oxadiazolyl, or -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen, CN, CF₃, -SO_n-C₁-6alkyl, or C₁-6alkyl substituents, and the alkyl group is optionally substituted with OH

- 5 R₅ is hydrogen, hydroxyl, -CN; or a -C₁-6alkyl, -C(O)C₁-6alkyl, -C(O)-aryl, -C(O)-pyridyl, -C(O)-O-C₀-6alkyl, -C(O)-C₃-7cycloalkyl, -C₁-6alkyl-C₃-7cycloalkyl, -C₁-6alkyl(C₃-7cycloalkyl)₂, -C₁-6alkyl-aryl, -C(O)-N(C₀-6alkyl)₂, -SO_naryl, -SO_n-C₁-6alkyl, -SO_n-C₃-7cycloalkyl, -SO_n-N(C₀-6alkyl)₂, -P(O)(C₁-6alkyl)₂, -P(O)(C₁-6alkoxy)₂, phenyl, pyridyl, -SO_nimidazolyl, -SO_nthiazolyl, 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N or oxoisoxaphosphinanyl group, any of which group optionally substituted with 1-6 independent halogen, hydroxyl, -CN, -CF₃, -C₁-6alkyl, -SO_n-C₁-6alkyl, -C(O)-O-C₀-6alkyl, or hydroxyC₁-6alkyl substituents;
- 10 or R₅ and R₆ form =O;
- 15 or R₆ and R₃ form -CH₂- or -O-; and
- n is 0, 1, or 2.

- 2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar is phenyl optionally substituted with 1-5 independent -C₁-6alkyl, -OH, -CN, halogen, -CF₃, -(C₀-6alkyl)-SO_n-(C₁-6alkyl), -(C₀-6alkyl)-SO_n-NH-(C₁-6alkyl) or 5-membered heteroaryl ring containing 1-4 heteroatoms independently selected from O, S or N, wherein the 5-membered-ring is optionally substituted with C₁-6alkyl, and the alkyl group- is optionally substituted with 1-3 independent -OH, -CN, halogen, or -CF₃.

- 25
- 3. The compound according to Claim 2, or a pharmaceutically acceptable salt thereof, wherein R₄ is hydrogen, halogen, -CN, or -C(O)-O-C₀-6alkyl, wherein the -C(O)-O-C₀-6alkyl is optionally substituted with 1-3 independent halogen or C₁-4alkyl substituents.

- 30
- 4. The compound according to Claim 2, or a pharmaceutically acceptable salt thereof, wherein R₄ is oxadiazolyl optionally substituted with 1-3 independent halogen or C₁-4alkyl substituents.

5. The compound according to Claim 2, or a pharmaceutically acceptable salt thereof, wherein R₆ and R₃ form -CH₂-.

6. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Ar is pyridyl or pyridyl N-oxide.

7. The compound according to Claim 6, or a pharmaceutically acceptable salt thereof, wherein R₄ is phenyl optionally substituted with 1-3 independent halogen or C₁₋₄alkyl substituents.

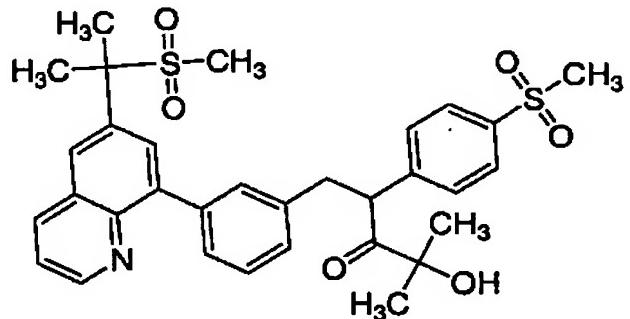
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8. The compound according to Claim 6, or a pharmaceutically acceptable salt thereof, wherein R₄ is hydrogen, halogen, -CN, or -C(O)-O-C₀₋₆alkyl, wherein the -C(O)-O-C₀₋₆alkyl is optionally substituted with 1-3 independent halogen or C₁₋₄alkyl substituents.

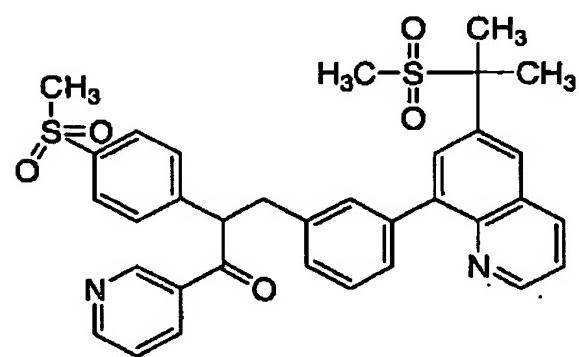
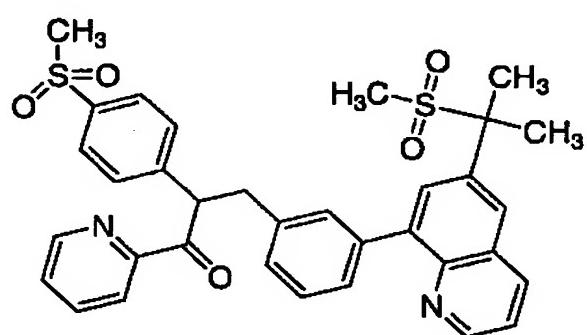
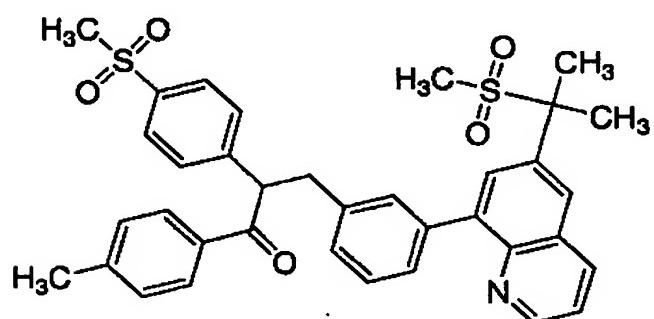
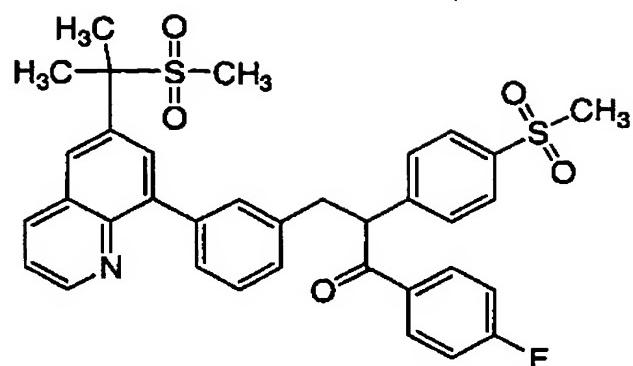
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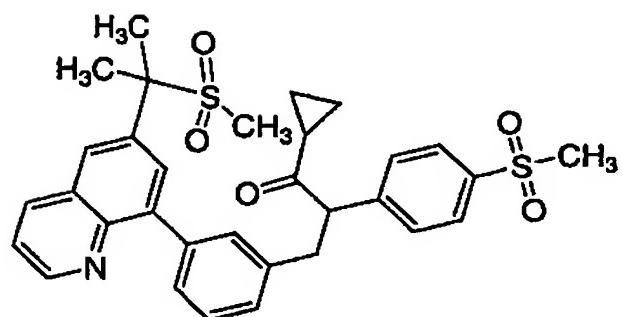
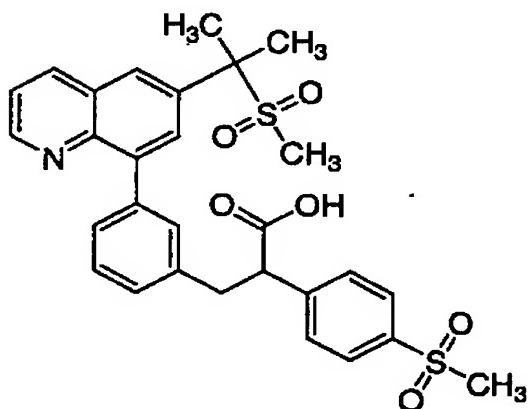
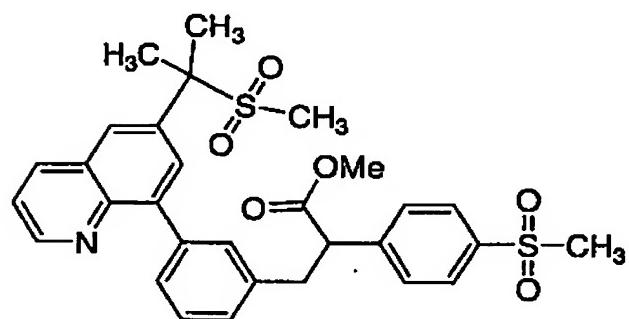
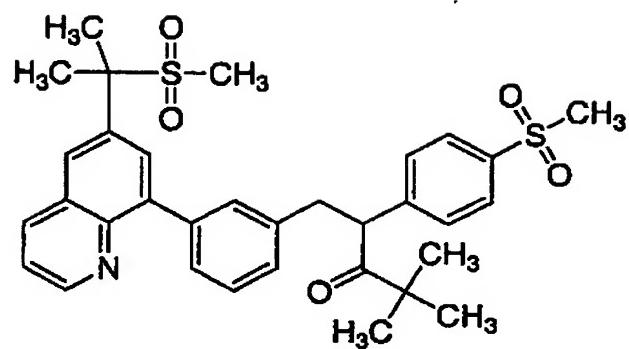
9. The compound according to Claim 6, or a pharmaceutically acceptable salt thereof, wherein R₆ and R₃ form -O-.

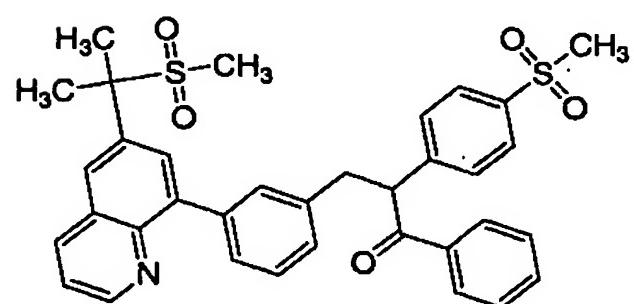
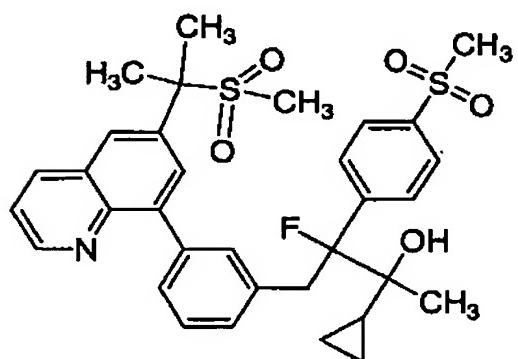
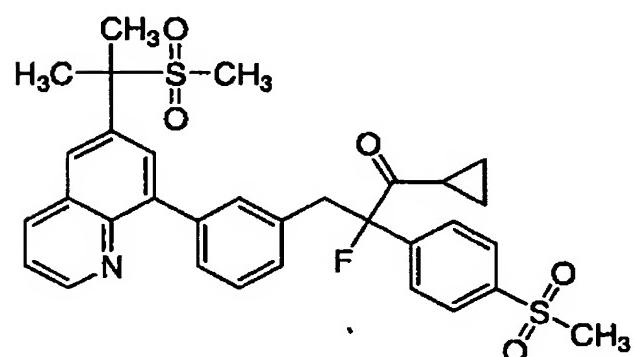
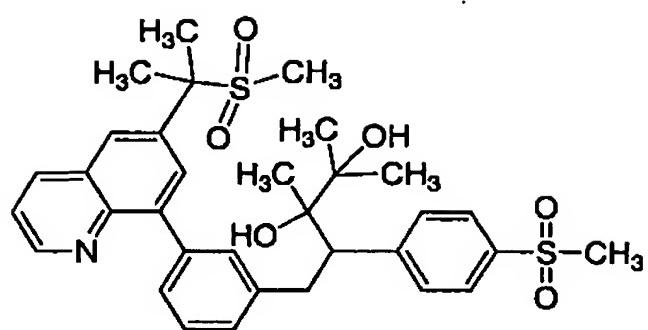
10. The compound according to Claim 1, represented by

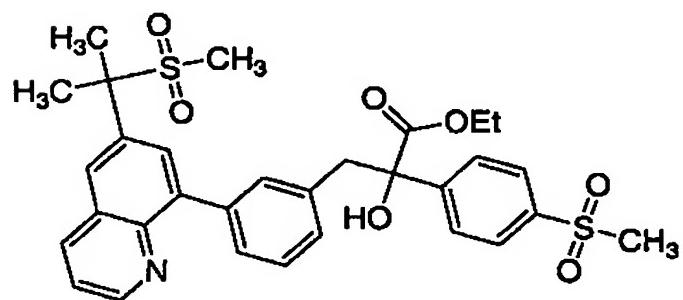
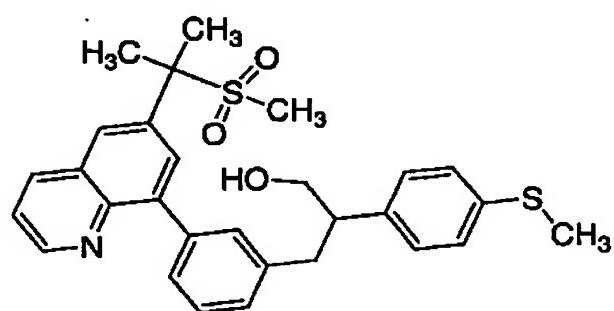
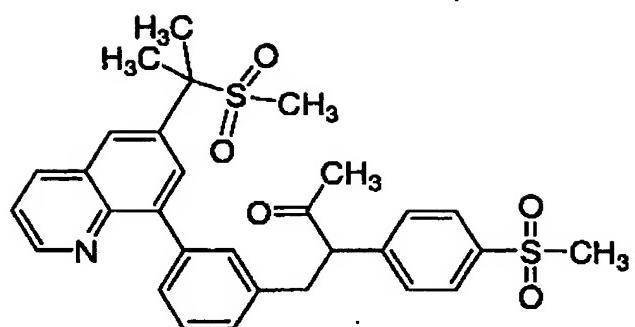


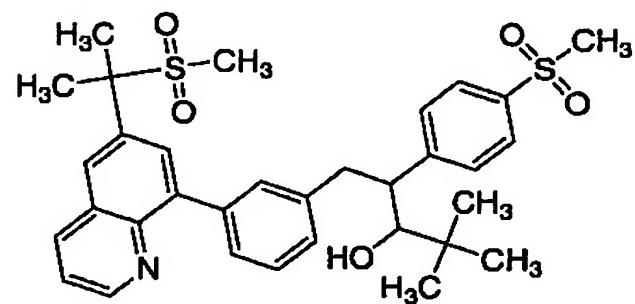
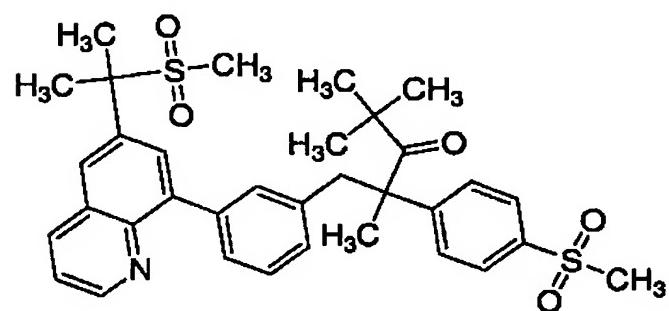
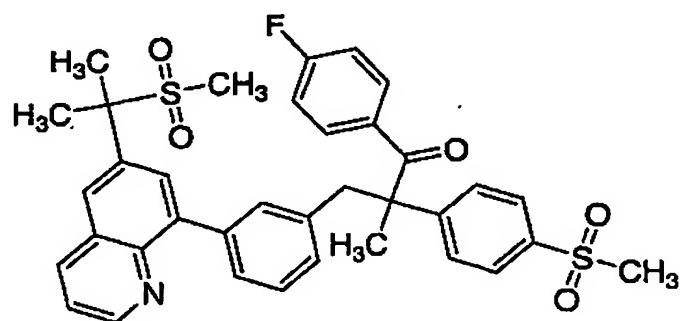
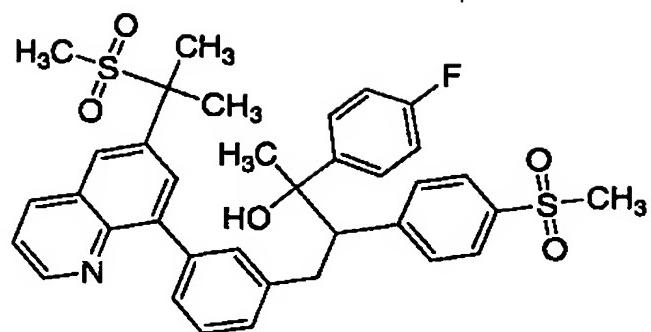
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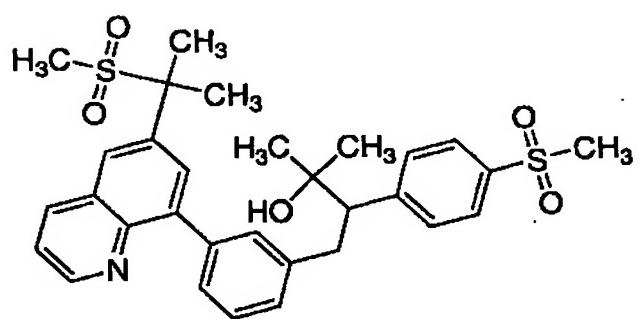
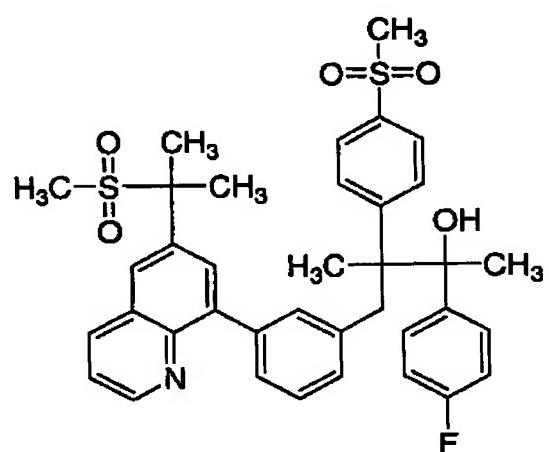
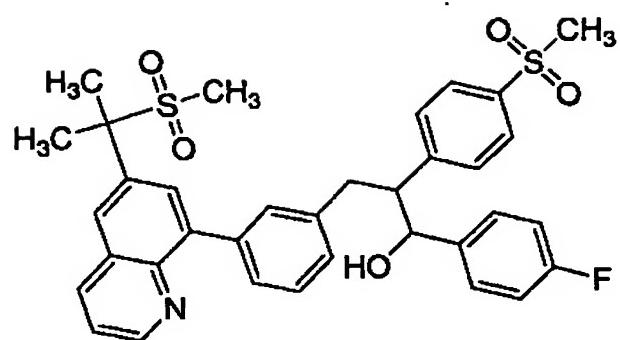


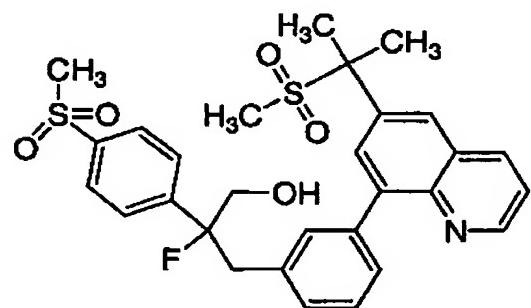
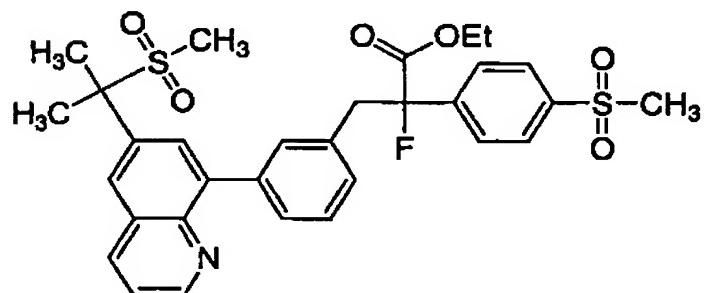
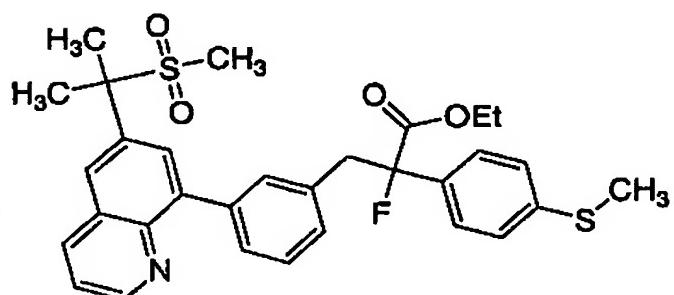
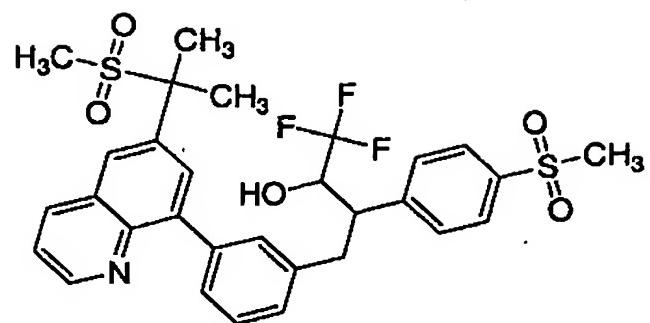


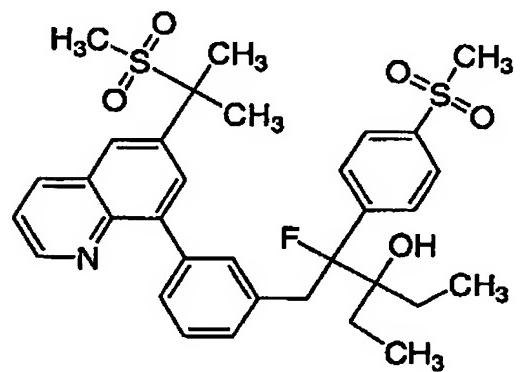
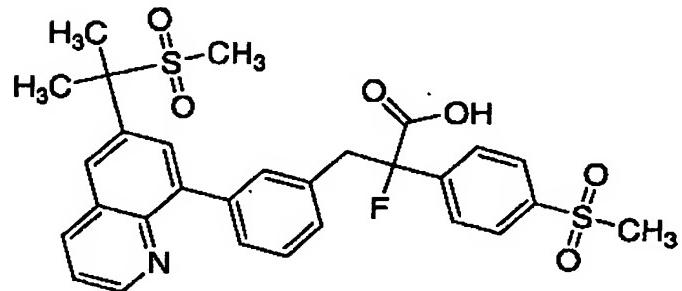
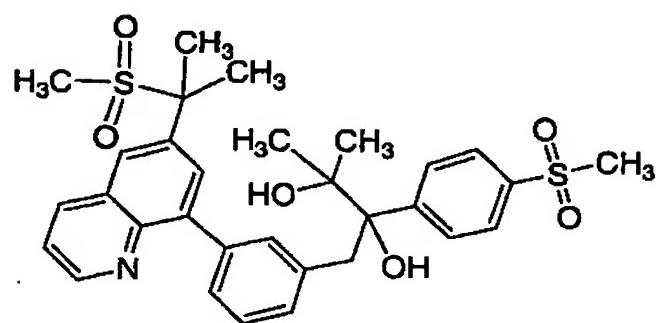
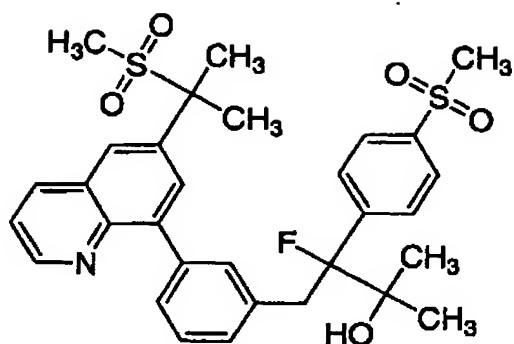


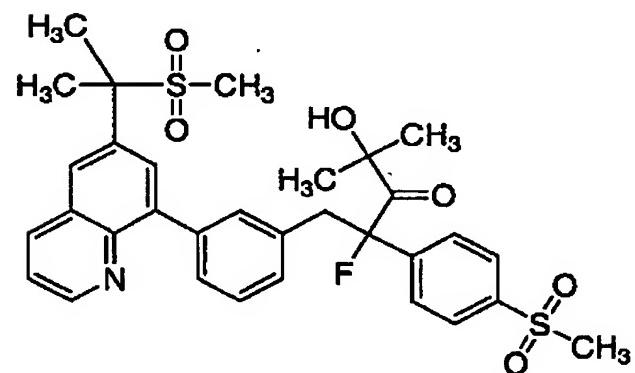
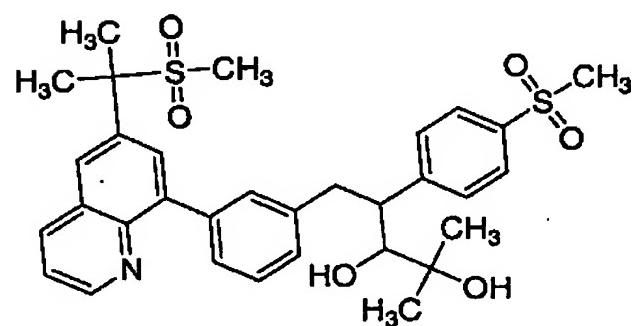
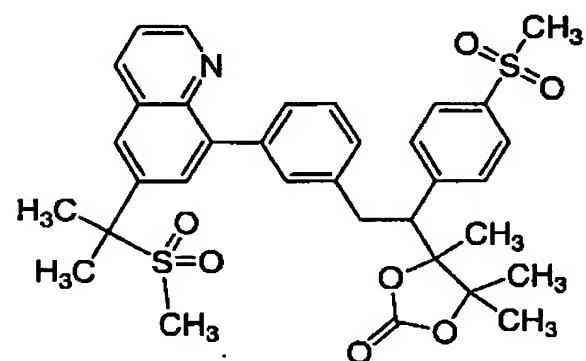
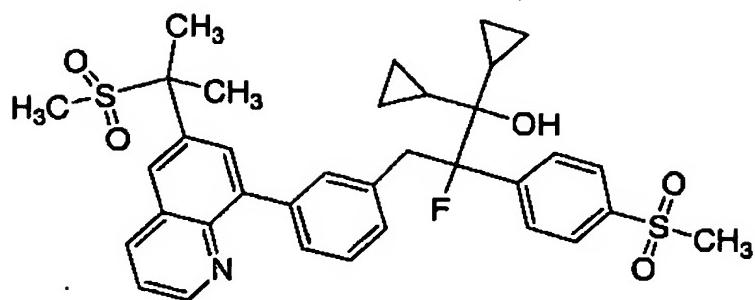


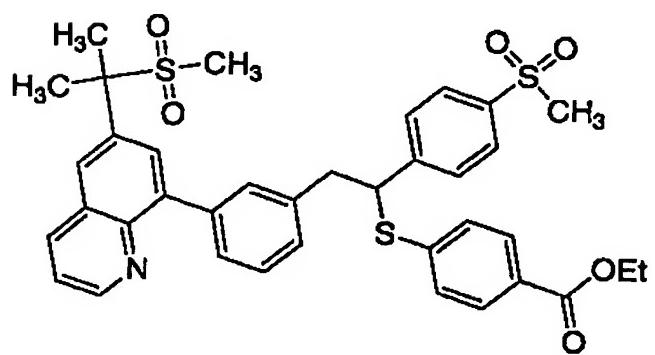
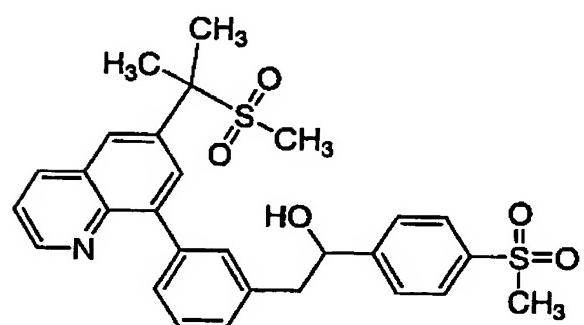
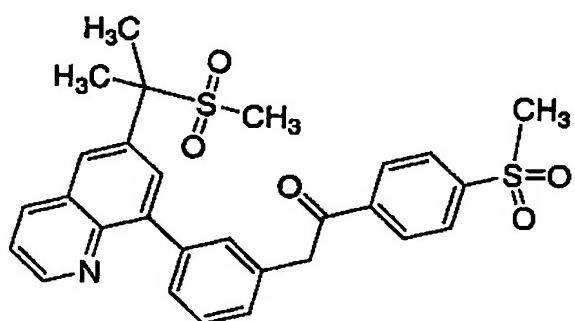
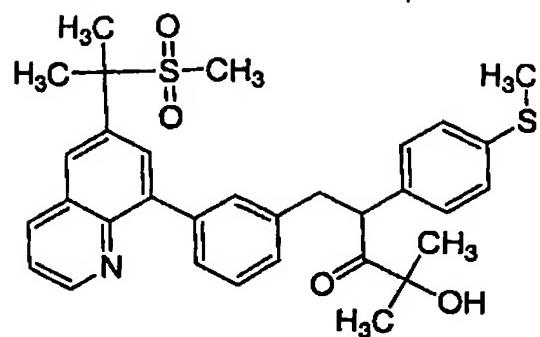


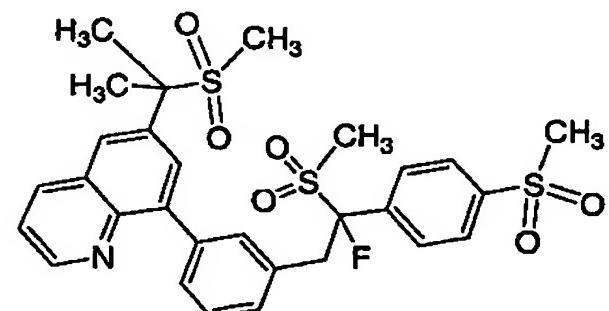
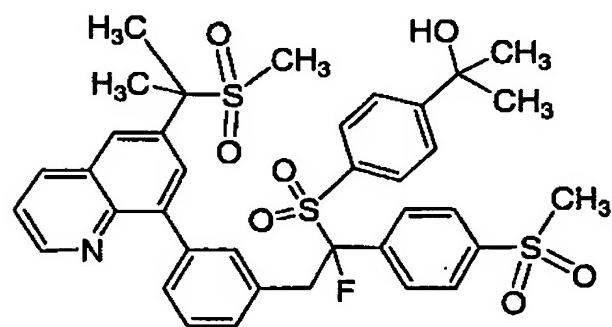
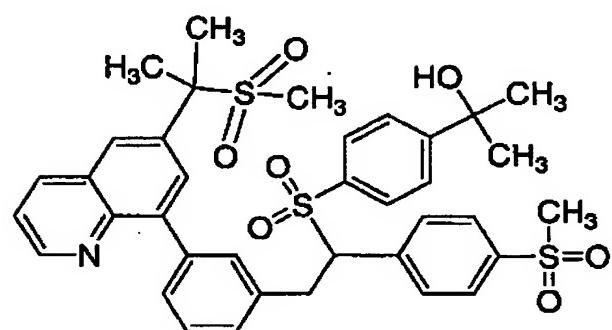
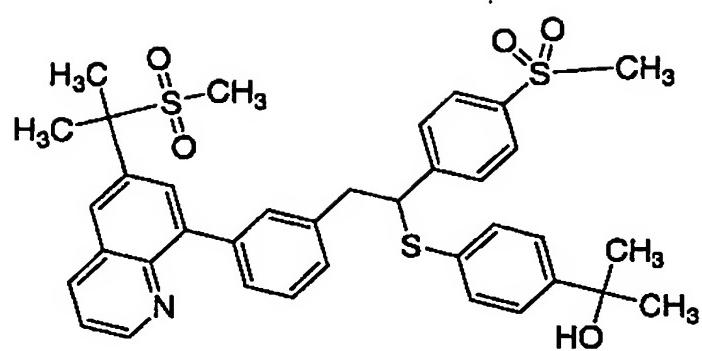


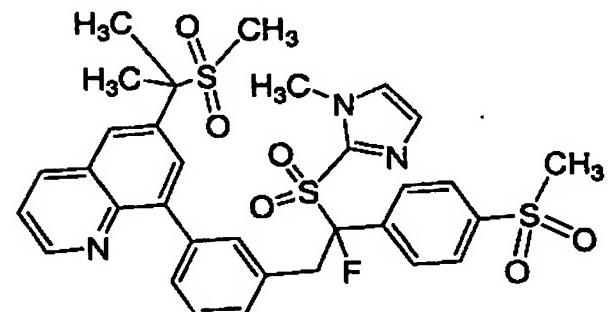
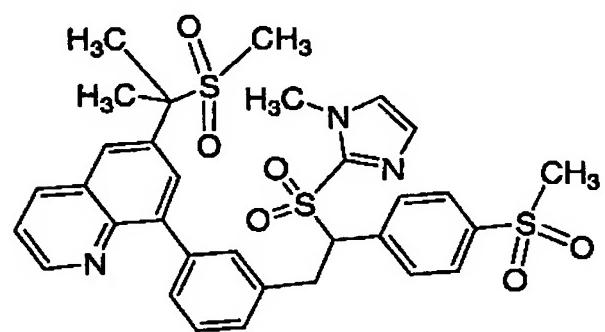
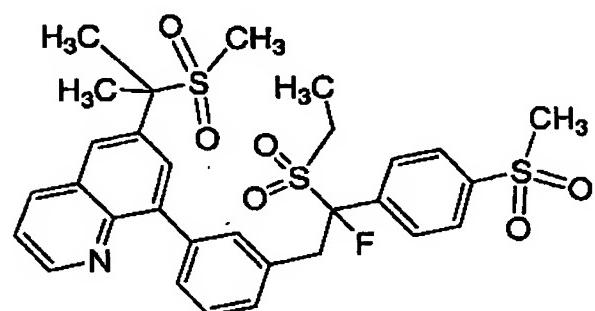
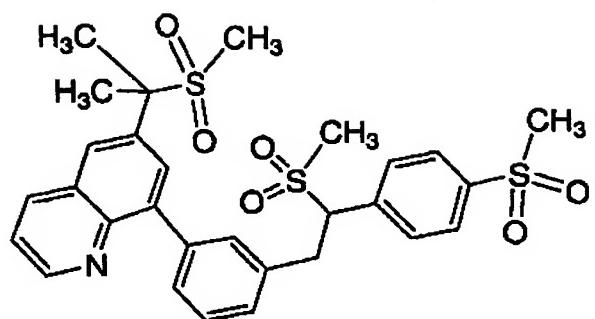


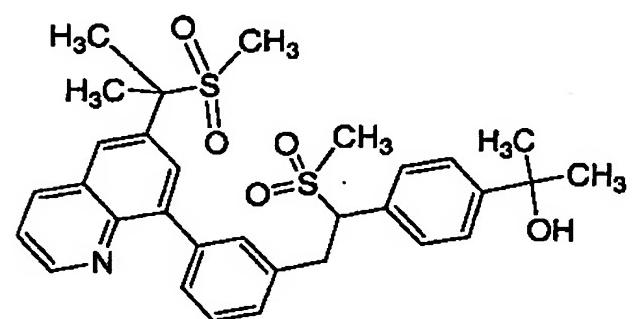
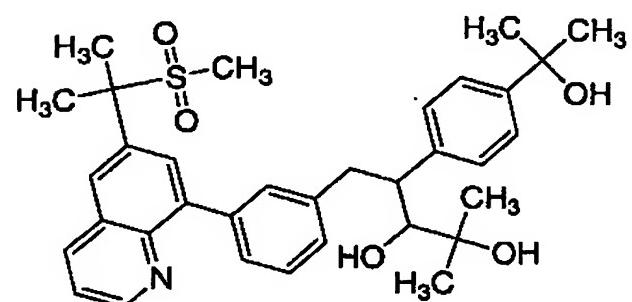
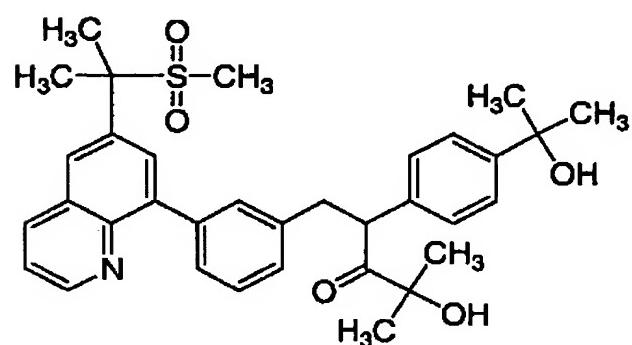
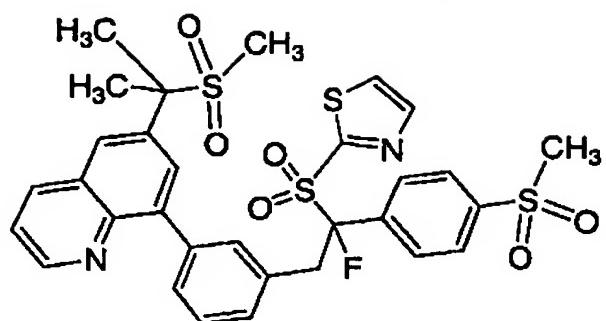


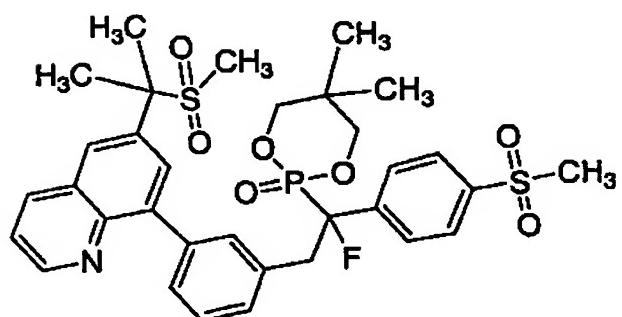
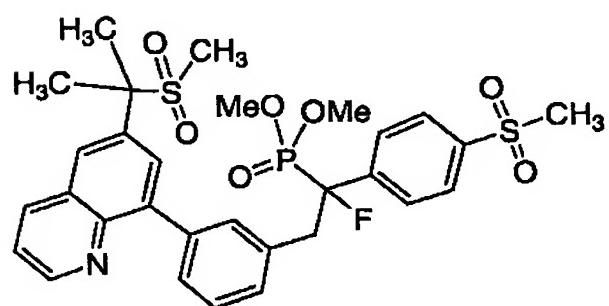
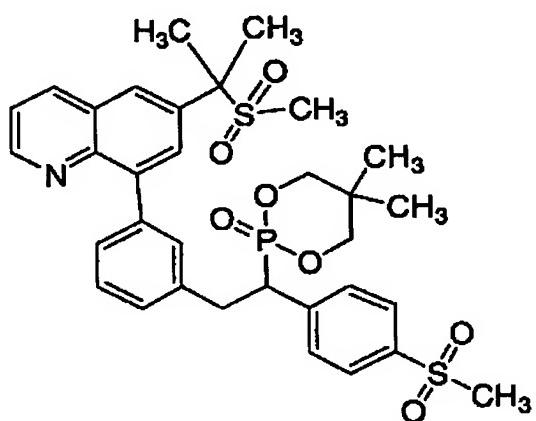
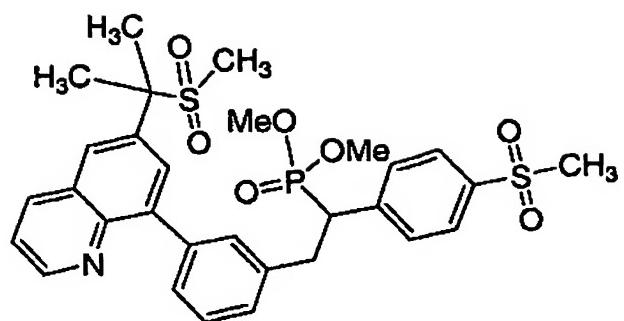


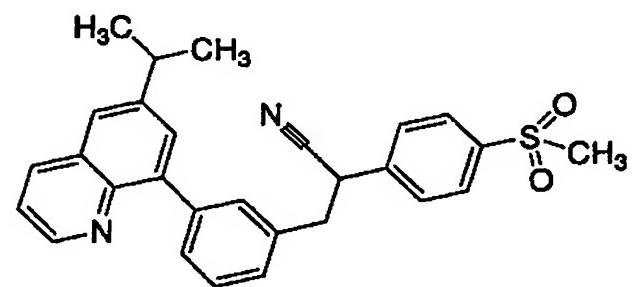
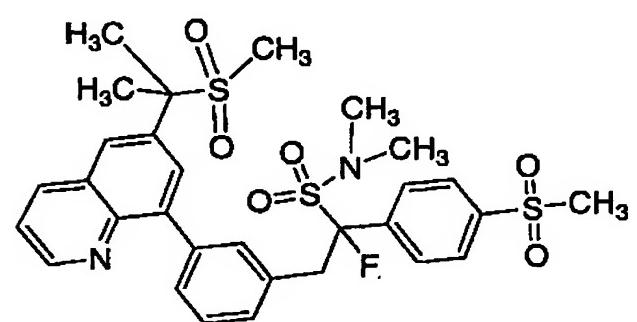
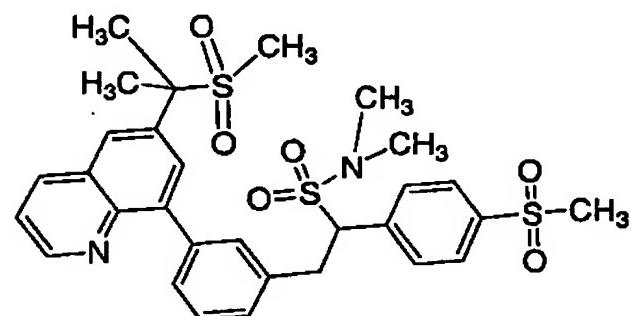
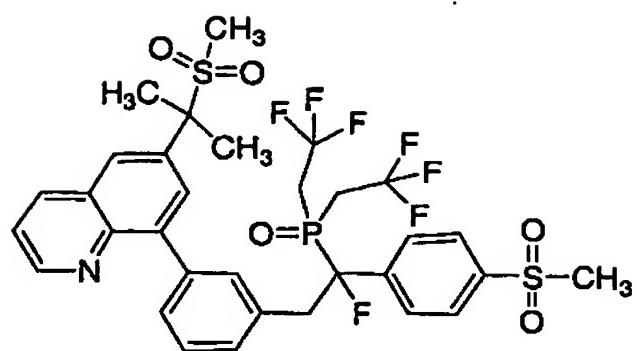


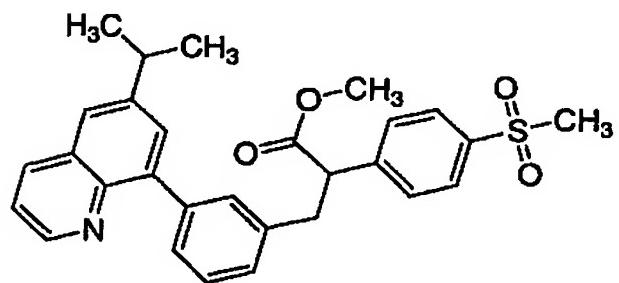
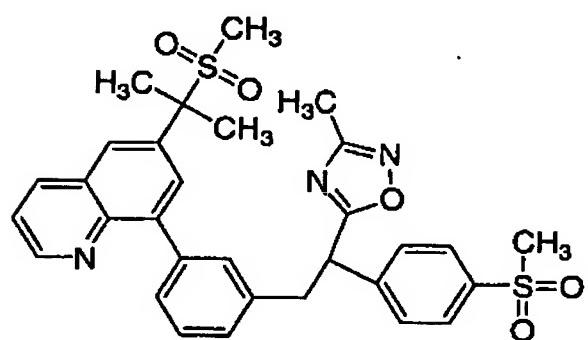
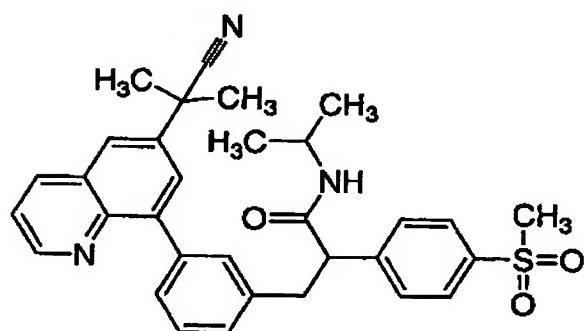
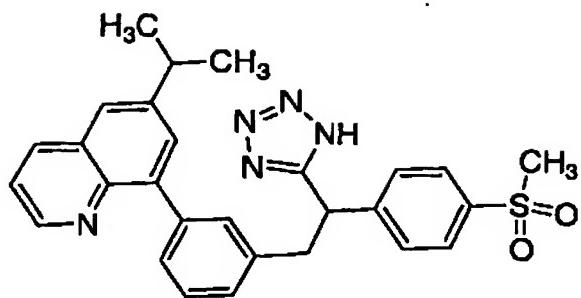


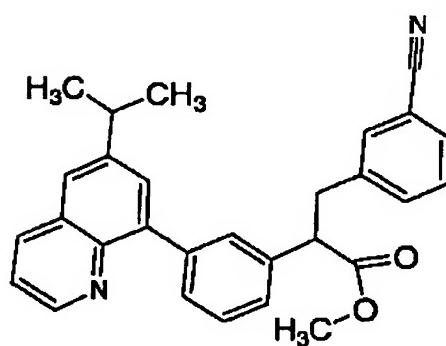
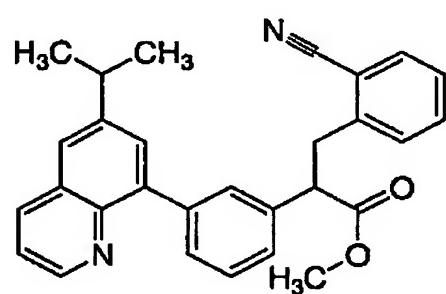
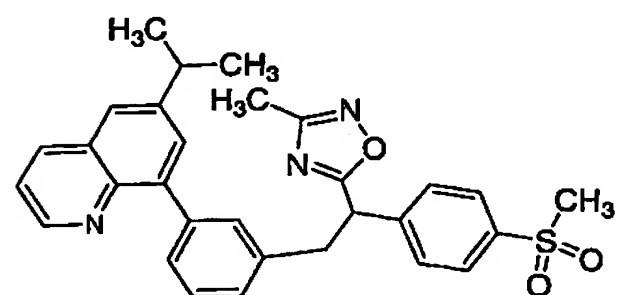
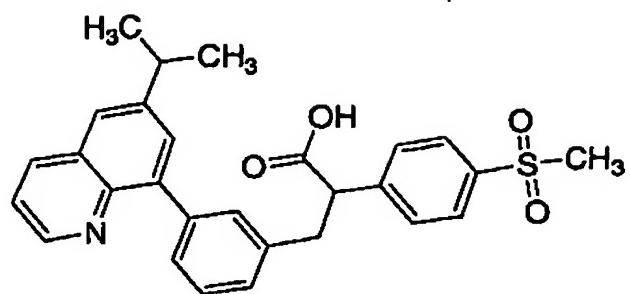


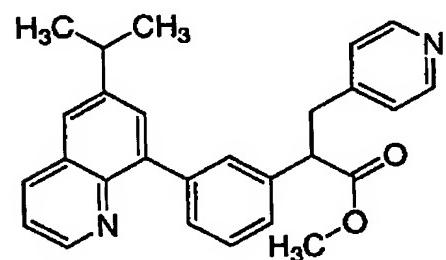
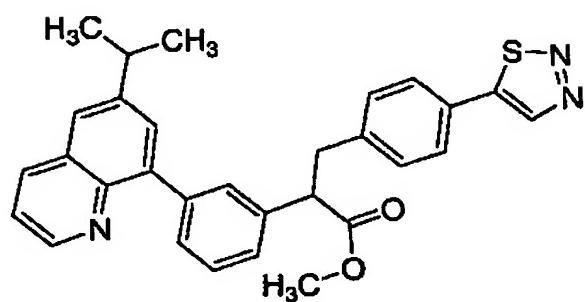
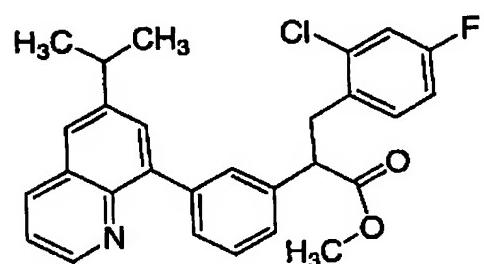
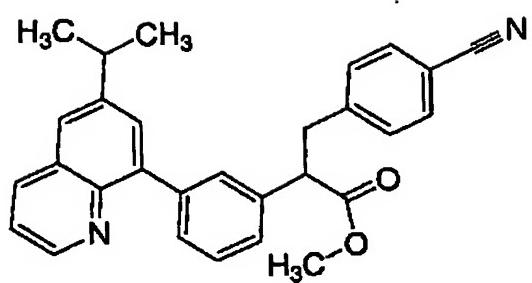


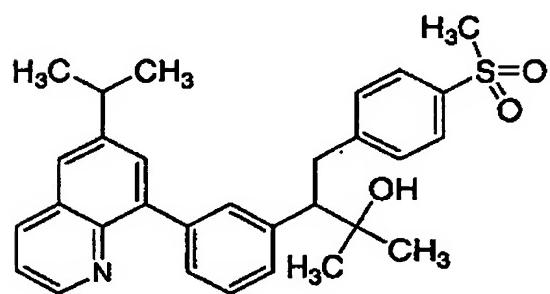
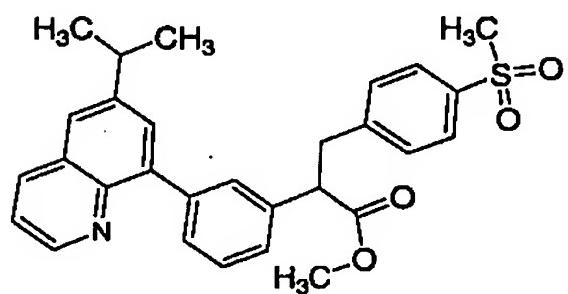
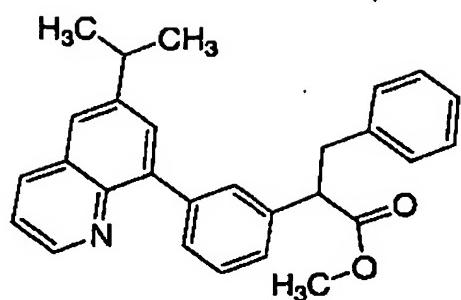


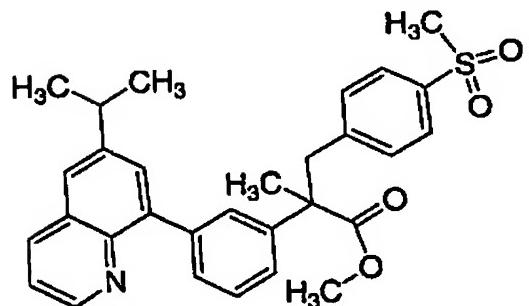
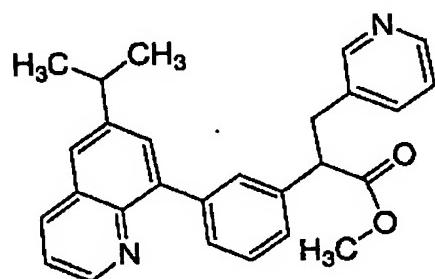
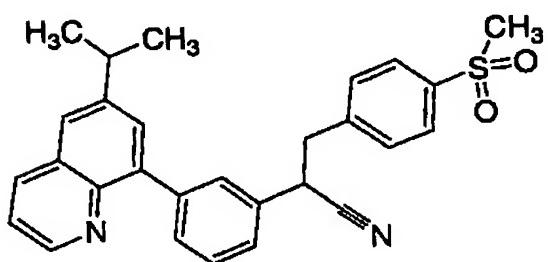
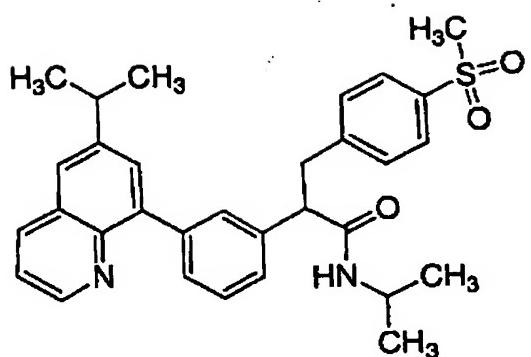


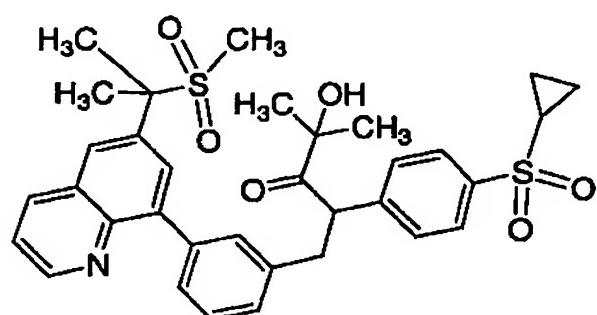
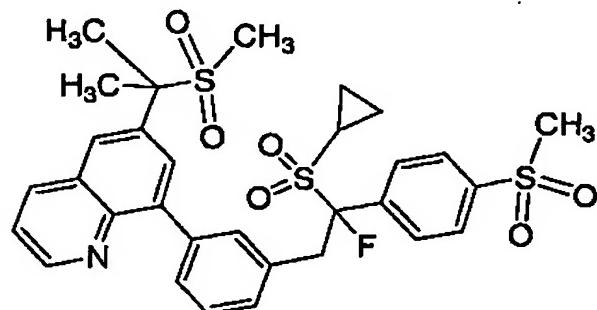
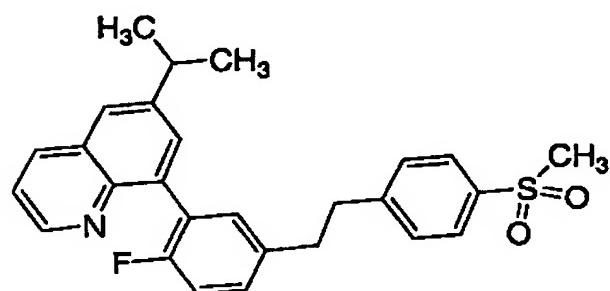
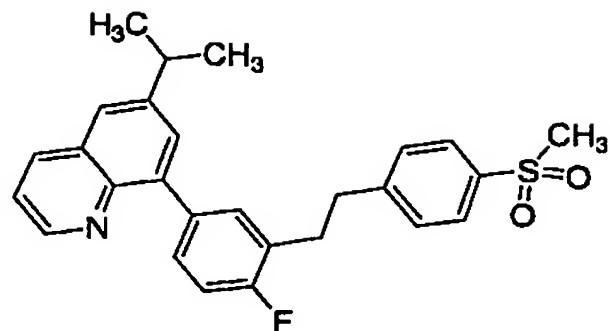


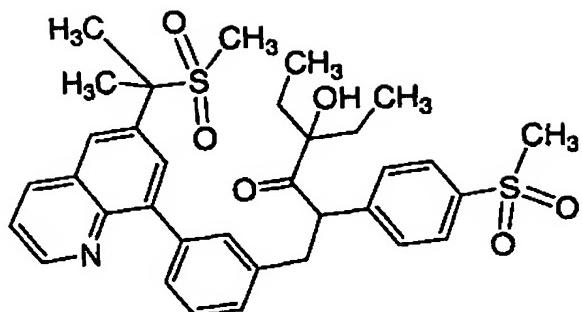






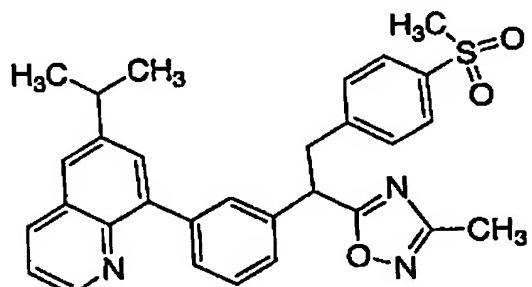






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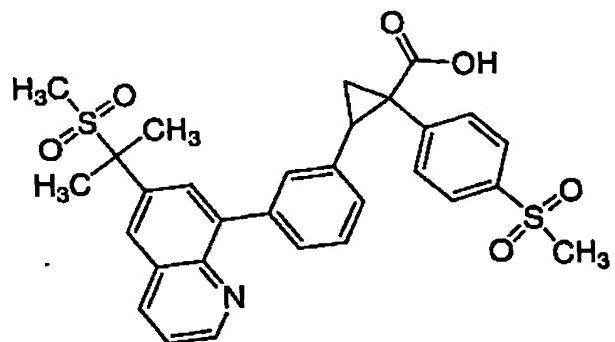
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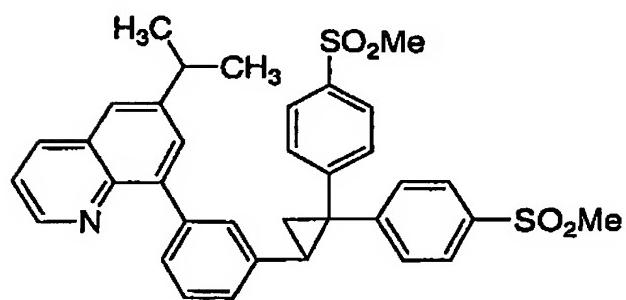
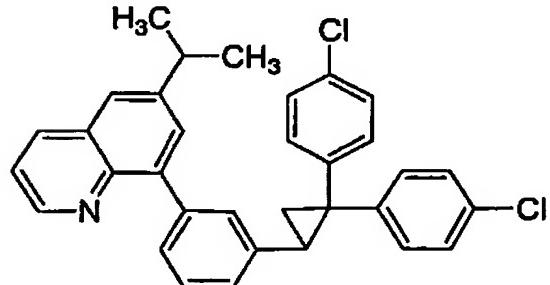
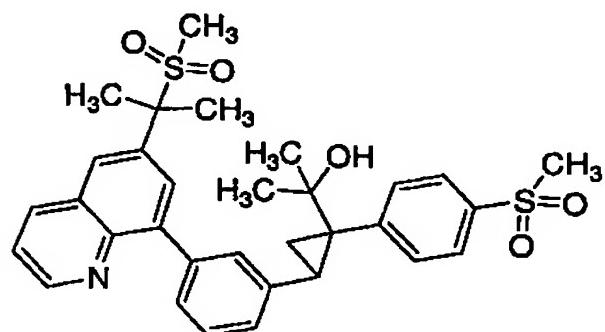
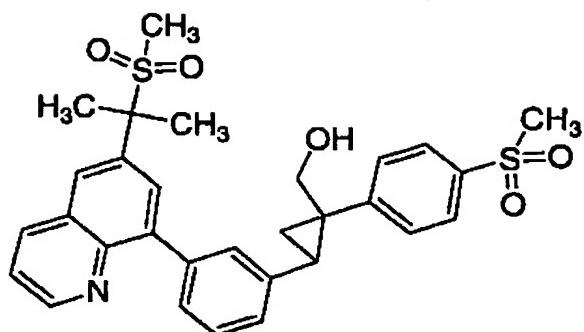


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or a pharmaceutically acceptable salt thereof.

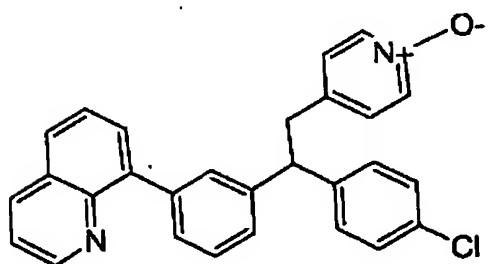
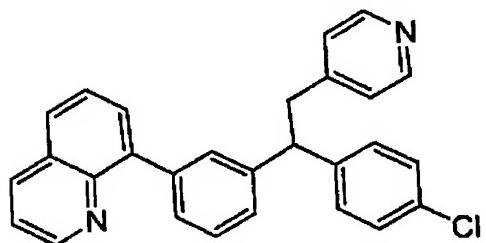
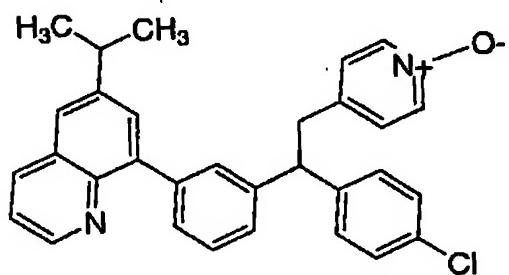
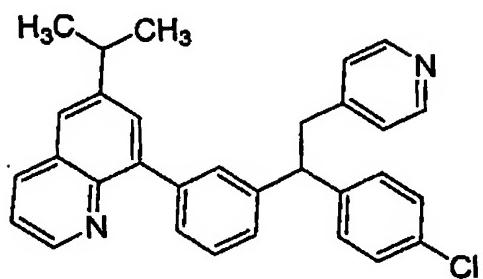
12. The compound according to Claim 1 represented by

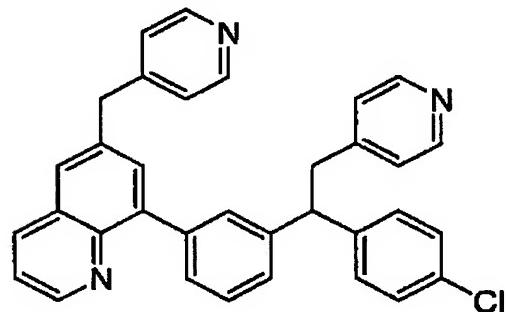
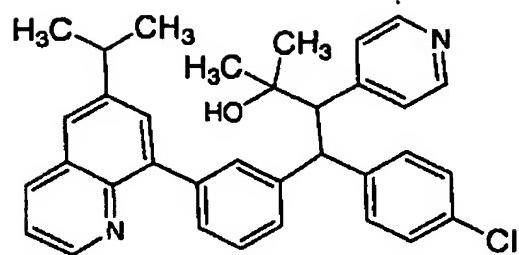




5 or a pharmaceutically acceptable salt thereof.

13. The compound according to Claim 1 represented by

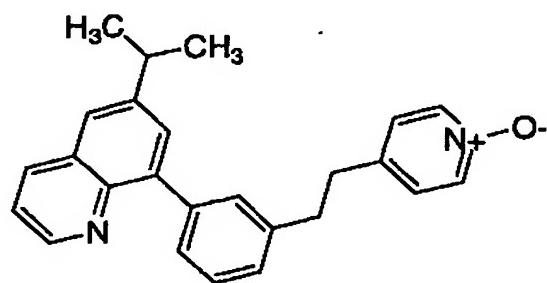
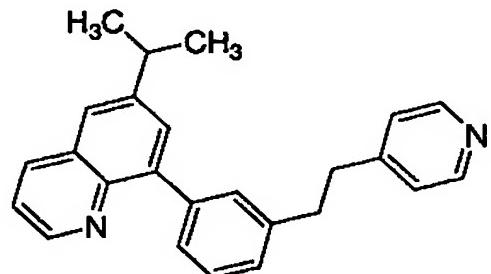


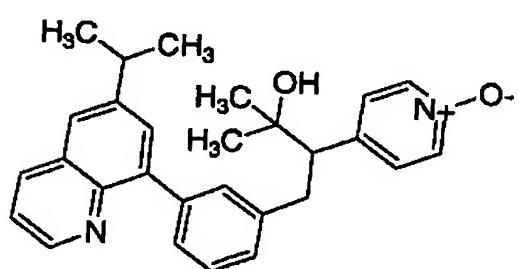
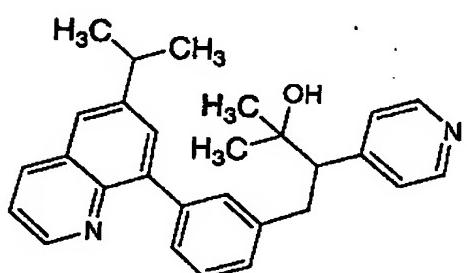
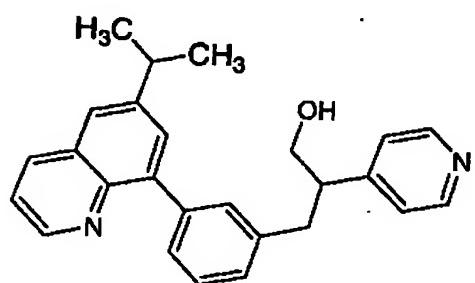
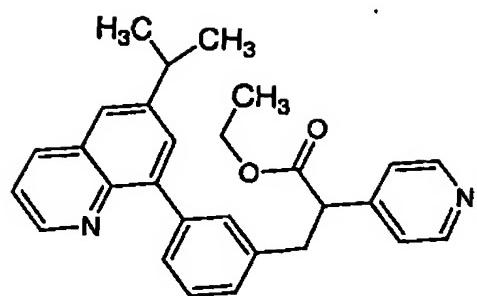


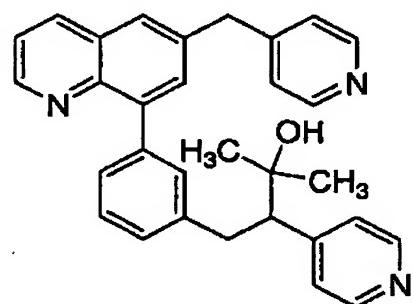
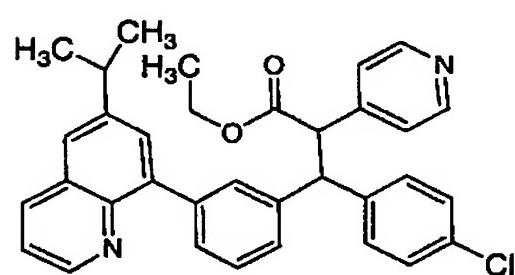
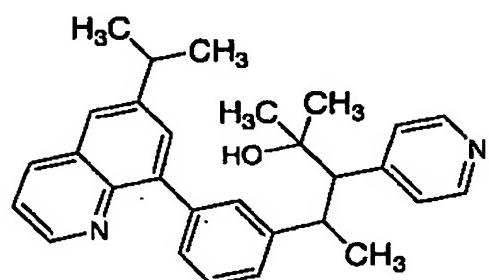
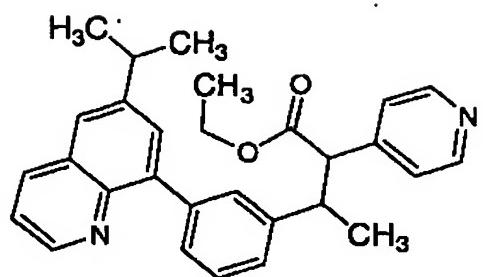
or a pharmaceutically acceptable salt thereof.

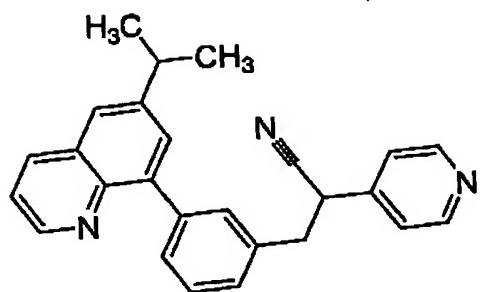
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14. The compound according to Claim 1 represented by



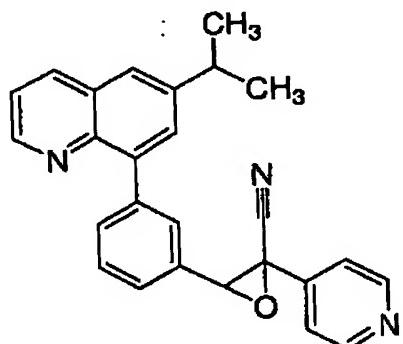




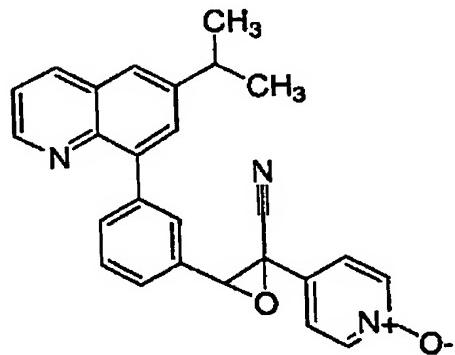


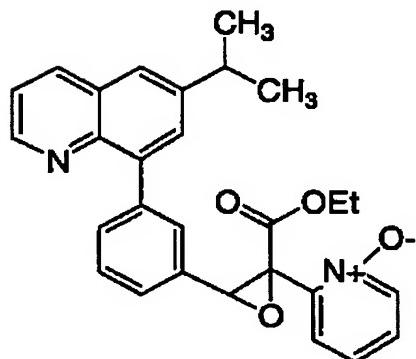
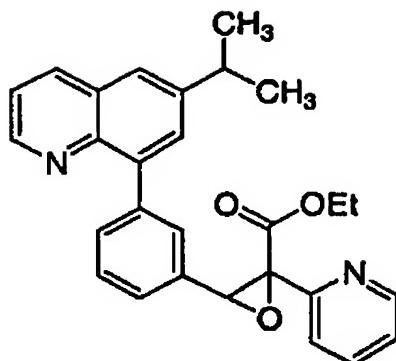
or a pharmaceutically acceptable salt thereof.

15. The compound according to Claim 1 represented by



5





or a pharmaceutically acceptable salt thereof.

5 **16. A pharmaceutical composition comprising a therapeutically effective amount of**

the compound according to any one of claims 1 to 15 or a pharmaceutically acceptable salt thereof; and
a pharmaceutically acceptable carrier.

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17. The pharmaceutical composition according to claim 16, further comprising a Leukotriene receptor antagonist, a Leukotriene biosynthesis inhibitor, an M2/M3 antagonist, a corticosteroid, an H1 receptor antagonist or a beta 2 adrenoceptor agonist.

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18. The pharmaceutical composition according to claim 16, further comprising a COX-2 selective inhibitor, a statin, or an NSAID.

19. A method of treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, comprising the step of 5 administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.
20. A method of treatment or prevention of eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic 10 dermatitis comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.
- 15 21. A method of treatment or prevention of laminitis in horses, or colic in horses comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.
- 20 22. A method of treatment or prevention of endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, comprising the 25 step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.
- 30 23. A method of treatment or prevention of Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

24. A method of treatment or prevention of adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

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25. A method of treatment or prevention of monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis comprising the step of administering a therapeutically effective amount, or a prophylactically effective amount, of the compound according to claim 1 or a pharmaceutically acceptable salt thereof.

26. A compound according to any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof for use in treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic dermatitis, laminitis in horses, or colic in horses, endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, orthosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis.

27. Use of a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament of treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic dermatitis, laminitis in horses, or colic in horses, endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue

degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis.

28. A pharmaceutical composition for treatment or prevention of asthma, chronic bronchitis, or chronic obstructive pulmonary disease, eosinophilic granuloma, psoriasis and other benign or malignant proliferative skin diseases, or atopic dermatitis, laminitis in horses, or colic in horses, endotoxic shock, septic shock, ulcerative colitis, bacterial or fungal induced sepsis, viral induced sepsis, bacterial or fungal induced septic shock, or viral induced septic shock, Crohn's disease, reperfusion injury of the myocardium and brain, inflammatory arthritis, chronic glomerulonephritis, urticaria, rheumatoid arthritis, transplant rejection, graft versus host disease, inflammation-mediated chronic tissue degeneration, cytokine-mediated chronic tissue degeneration, osteoarthritis, or muscle wasting, adult respiratory distress syndrome, chronic obstructive pulmonary disease in animals, diabetes insipidus, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, ortherosclerosis, atherosclerosis, neurogenic inflammation, pain, cough, ankylosing spondylitis, hypersecretion of gastric acid, cancer, cachexia, depression, memory impairment, tumour growth, or cancerous invasion of normal tissues, monopolar depression, acute and chronic neurodegenerative disorders with inflammatory components, Parkinson disease, Alzheimer's disease, spinal cord trauma, head injury, or multiple sclerosis comprising a compound of any one of claims 1 to 15, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/CA 02/00953

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	A61K31/47	C07D215/12	C07D401/10	C07D405/10	C07D417/12
	C07F9/60	C07F9/6571	C07D403/10	C07D413/10	C07D417/10
	C07D405/14	A61P11/06	A61P29/00	A61P17/06	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 46151 A (MASTRACCHIO ANTHONY ;MERCK FROSST CANADA INC (CA); DUBE DANIEL (CA) 28 June 2001 (2001-06-28) claim 1 -----	1-28
A	US 5 455 252 A (WILHELM ROBERT S ET AL) 3 October 1995 (1995-10-03) claim 1 -----	1-28



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the International search

2 September 2002

Date of mailing of the International search report

17/09/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 02/00953

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 19-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Application No
PCT/CA 02/00953

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0146151	A 28-06-2001	AU	2336201 A	03-07-2001
		WO	0146151 A1	28-06-2001
		US	6410563 B1	25-06-2002
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